VOL. 16 NO. 2 APRIL, 1959

BRITISH JOURNAL OF INDUSTRIAL MEDICINE

EDITOR
L. G. NORMAN
ASSISTANT EDITORS
J. M. BARNES J. C. GILSON

CONTENTS

PAGE

Health Problems of Epoxy Resins and Amine-curing Agents. L. B. BOURNE, F. J. MILNER, and K. B. ALBERMAN 81

Medical Examinations for Public Safety. P. A. B. RAFFLE 98

Measuring Dust Exposure with the Thermal Precipitator in Collieries and Foundries. S. A. ROACH 104

Pulmonary Fibrosis in an Aluminium Worker. JOHN MITCHELL 123

Two Cases of Hydrazine Hydrate Dermatitis without Systemic Intoxication. DARRELL M. EVANS 126

The Chemotherapy of Poisoning by Organophosphate Anticholinesterases. D. R. DAVIES and A. L. GREEN 128

A Follow-up Study of Men Exposed to Cadmium Oxide Fume. J. A. BONNELL, G. KAZANTZIS, and E. KING 135

The Value of Mobilization of Lead by Calcium Ethylene-diamine-tetra-acetate in the Diagnosis of Lead Poisoning. J. TEISINGER and J. SRBOVÁ 148

The Mechanical Properties of the Lung in Pneumoconiosis of Coal-miners. G. L. LEATHART 153

Further Studies of the Neutralization of Silica Toxicity *In Vitro*. J. MARKS 166

Miscellanea:

The Employment of Diabetics. JOHN F. COPPLESTONE.. 170

Book Reviews 175

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

YEARLY SUBSCRIPTION (4 NUMBERS) £3. U.S.A. $10.00 SINGLE NUMBER 17/6

EDITORIAL COMMITTEE

THOMAS BEDFORD
SIR ROY CAMERON
C. M. FLETCHER
M. W. GOLDBLATT
ALASTAIR HERON
A. BRADFORD HILL
T. G. FAULKNER HUDSON
R. E. LANE
J. F. LOUTIT
H. B. MAITLAND
A. MEIKLEJOHN
J. N. MORRIS
R. S. F. SCHILLING
J. A. SMILEY
J. R. SQUIRE
EDITOR, *British Medical Journal*

GENERAL ADVISORY BOARD

A. J. AMOR
SIR FREDERIC BARTLETT
SIR HENRY BASHFORD
G. P. CROWDEN
DONALD HUNTER
SIR WILSON JAMESON
T. A. LLOYD-DAVIES
J. M. MACKINTOSH
E. R. A. MEREWETHER
D. C. NORRIS
H. OSMOND-CLARKE
K. M. A. PERRY
DONALD STEWART
SIR REGINALD WATSON-JONES

President of the Association of Industrial Medical Officers and Hon. Editor of the Transactions of the Association of Industrial Medical Officers, *ex officio*

NOTICE TO CONTRIBUTORS

The *British Journal of Industrial Medicine* is intended for the publication of original contributions in industrial medicine from workers of any nationality. It also provides a section for book reviews.

All papers submitted for publication should be referred to The Editor, British Journal of Industrial Medicine, Griffith House, 280 Marylebone Road, London, N.W.1.

Papers are accepted on the understanding that they are contributed solely to this Journal, and that they are subject to editorial revision. Papers should be prefaced by an abstract of the argument and findings and should be more comprehensive than a summary which will not be required. Papers must be typewritten on one side of the paper only, with double spacing, and with a margin of at least $1\frac{1}{4}$ in. Photographs and photomicrographs should be printed on glossy paper, and should be unmarked. Charts and graphs accompanying papers should be carefully drawn in black ink on tracing linen or Bristol board or stout, smooth, white paper. Any lettering on these drawings to be done in the editorial office should be lightly inserted in pencil.

References should be arranged according to the Harvard system. When a book is referred to, the place and year of publication, edition, and page should be given. In the text the year of publication must follow the author's name, more than one paper in any one year being indicated by a small letter (a, b, c) after the date. No numbering of references is necessary.

Contributors will receive one proof, but it is assumed that all but verbal corrections have been made in the original manuscript; an allowance at the rate of 10s. per sheet of 16 pages is made for alterations in the proof (printer's errors excepted), and contributors will be responsible for any excess.

Twenty-five free reprints of articles will, if desired, be given to contributors. A limited number of additional reprints at cost price can be supplied if application is made when returning proofs. An estimate of costs will be given on application to the Publishing Manager, British Medical Association.

Papers which have been published become the property of the *British Journal of Industrial Medicine* and permission to republish must be obtained from the Editor.

Application for advertisement space should be addressed to the Advertisement Manager, British Medical Association, Tavistock Square, London, W.C.1.

NOTICE TO SUBSCRIBERS

Subscriptions are payable to the British Medical Association. Address: British Medical Association House, Tavistock Square, London, W.C.1.

PREDSOL

THE WATER-SOLUBLE PREDNISOLONE

PREPARATION	BASE	PACKS	INDICATIONS
Predsol Lotion 0·1	Water-miscible	20 ml	Atopic and solar prurigo Contact dermatitis Seborrhoeic dermatitis Allergic eczema Nummular dermatitis Pruritus vulvae Infantile eczema Neurodermatitis
0·25		20 ml	
Predsol-N* Lotion 0·1	Water-miscible	20 ml	
0·25		20 ml	
Predsol Ointment Nos. 1 & 2 0·25		5 G	
0·25	No. 1 non-greasy base	15 G	
0·5	No. 2 greasy base	5 G	
0·5		15 G	
Predsol-N* Ointment Nos. 1 & 2 0·25		5 G	
0·25	No. 1 non-greasy base	15 G	
0·5	No. 2 greasy base	5 G	
0·5		15 G	

*Contains 0·1% neomycin sulphate. The Predsol-N preparations are also available in packs of 50 ml.

A STRENGTH FOR EVERY PURPOSE A BASE FOR EVERY SURFACE

PREDSOL prednisolone 21-disodium phosphate (the water-soluble prednisolone)
PREDSOL-N prednisolone 21-disodium phosphate (the water-soluble prednisolone) neomycin sulphate

GLAXO LABORATORIES LTD. GREENFORD, MIDDLESEX. BYRON 1331

GLAXO

EDITORIAL COMMITTEE

THOMAS BEDFORD
SIR ROY CAMERON
C. M. FLETCHER
M. W. GOLDBLATT
ALASTAIR HERON
A. BRADFORD HILL
T. G. FAULKNER HUDSON
R. E. LANE
J. F. LOUTIT
H. B. MAITLAND
A. MEIKLEJOHN
J. N. MORRIS
R. S. F. SCHILLING
J. A. SMILEY
J. R. SQUIRE
EDITOR, *British Medical Journal*

GENERAL ADVISORY BOARD

A. J. AMOR
SIR FREDERIC BARTLETT
SIR HENRY BASHFORD
G. P. CROWDEN
DONALD HUNTER
SIR WILSON JAMESON
T. A. LLOYD-DAVIES
J. M. MACKINTOSH
E. R. A. MEREWETHER
D. C. NORRIS
H. OSMOND-CLARKE
K. M. A. PERRY
DONALD STEWART
SIR REGINALD WATSON-JONES

President of the Association of Industrial Medical Officers and Hon. Editor of the Transactions of the Association of Industrial Medical Officers, *ex officio*

NOTICE TO CONTRIBUTORS

The *British Journal of Industrial Medicine* is intended for the publication of original contributions in industrial medicine from workers of any nationality. It also provides a section for book reviews.

All papers submitted for publication should be referred to The Editor, British Journal of Industrial Medicine, Griffith House, 280 Marylebone Road, London, N.W.1.

Papers are accepted on the understanding that they are contributed solely to this Journal, and that they are subject to editorial revision. Papers should be prefaced by an abstract of the argument and findings and should be more comprehensive than a summary which will not be required. Papers must be typewritten on one side of the paper only, with double spacing, and with a margin of at least 1¼ in. Photographs and photomicrographs should be printed on glossy paper, and should be unmarked. Charts and graphs accompanying papers should be carefully drawn in black ink on tracing linen or Bristol board or stout, smooth, white paper. Any lettering on these drawings to be done in the editorial office should be lightly inserted in pencil.

References should be arranged according to the Harvard system. When a book is referred to, the place and year of publication, edition, and page should be given. In the text the year of publication must follow the author's name, more than one paper in any one year being indicated by a small letter (a, b, c) after the date. No numbering of references is necessary.

Contributors will receive one proof, but it is assumed that all but verbal corrections have been made in the original manuscript; an allowance at the rate of 10s. per sheet of 16 pages is made for alterations in the proof (printer's errors excepted), and contributors will be responsible for any excess.

Twenty-five free reprints of articles will, if desired, be given to contributors. A limited number of additional reprints at cost price can be supplied if application is made when returning proofs. An estimate of costs will be given on application to the Publishing Manager, British Medical Association.

Papers which have been published become the property of the *British Journal of Industrial Medicine* and permission to republish must be obtained from the Editor.

Application for advertisement space should be addressed to the Advertisement Manager, British Medical Association, Tavistock Square, London, W.C.1.

NOTICE TO SUBSCRIBERS

Subscriptions are payable to the British Medical Association. Address: British Medical Association House, Tavistock Square, London, W.C.1.

ALL-ROUND SUPPRESSION OF DERMATOSES

PREDSOL

THE WATER-SOLUBLE PREDNISOLONE

PREPARATION	BASE	PACKS	INDICATIONS
Predsol Lotion 0·1%	Water-miscible	20 ml	Anal and vulval pruritus Contact dermatitis Seborrhoeic dermatitis Allergic eczema Nummular dermatitis Food eczema Infantile eczema Neurodermatitis
0·25%		20 ml	
Predsol-N* Lotion 0·1%	Water-miscible	20 ml	
0·25%		20 ml	
Predsol Ointment Nos. 1 & 2 0·25%	No.1—non-greasy	5 G	
0·25%		15 G	
0·5%	No.2—greasy base	5 G	
0·5%		15 G	
Predsol-N* Ointment Nos. 1 & 2 0·25%	No.1—non-greasy	5 G	
0·25%		15 G	
0·5%	No.2—greasy base	5 G	
0·5%		15 G	

** Contains 0·5% neomycin sulphate. Use Predsol-N preparations when infection is present or suspected.*

A STRENGTH FOR EVERY PURPOSE A BASE FOR EVERY SURFACE

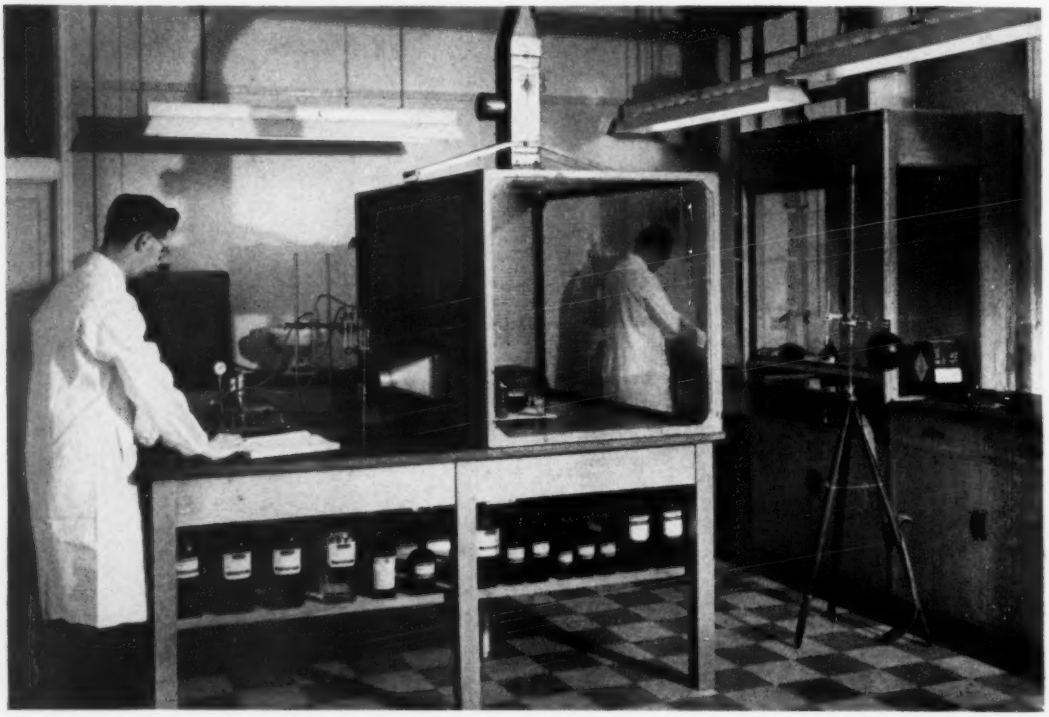
PREDSOL = prednisolone 21-disodium phosphate (the water-soluble prednisolone)

PREDSOL-N = prednisolone 21-disodium phosphate (the water-soluble prednisolone) + neomycin sulphate

PREDSOL and PREDSOL-N are British made

GLAXO

GLAXO LABORATORIES LTD, GREENFORD, MIDDLESEX BYRon 3434



OHS ***OCCUPATIONAL HYGIENE SERVICE***

A Consulting and Laboratory Service now extended to Industry throughout the country.

The following facilities are available

ENVIRONMENTAL
- ***Lighting surveys***
- ***Heating and ventilation studies***
- ***Noise measurements and analysis***

AIR CONTAMINATION
- ***Dust counts and particle size analysis***
- ***Dust analysis***
- ***Toxic gas, vapour and fume determinations***

CLINICAL-to-include
- ***Blood studies***
- ***Urine analysis***
- ***Audiometry***
- ***X-ray examinations***

Prospectus from the Secretary

OCCUPATIONAL HYGIENE SERVICE

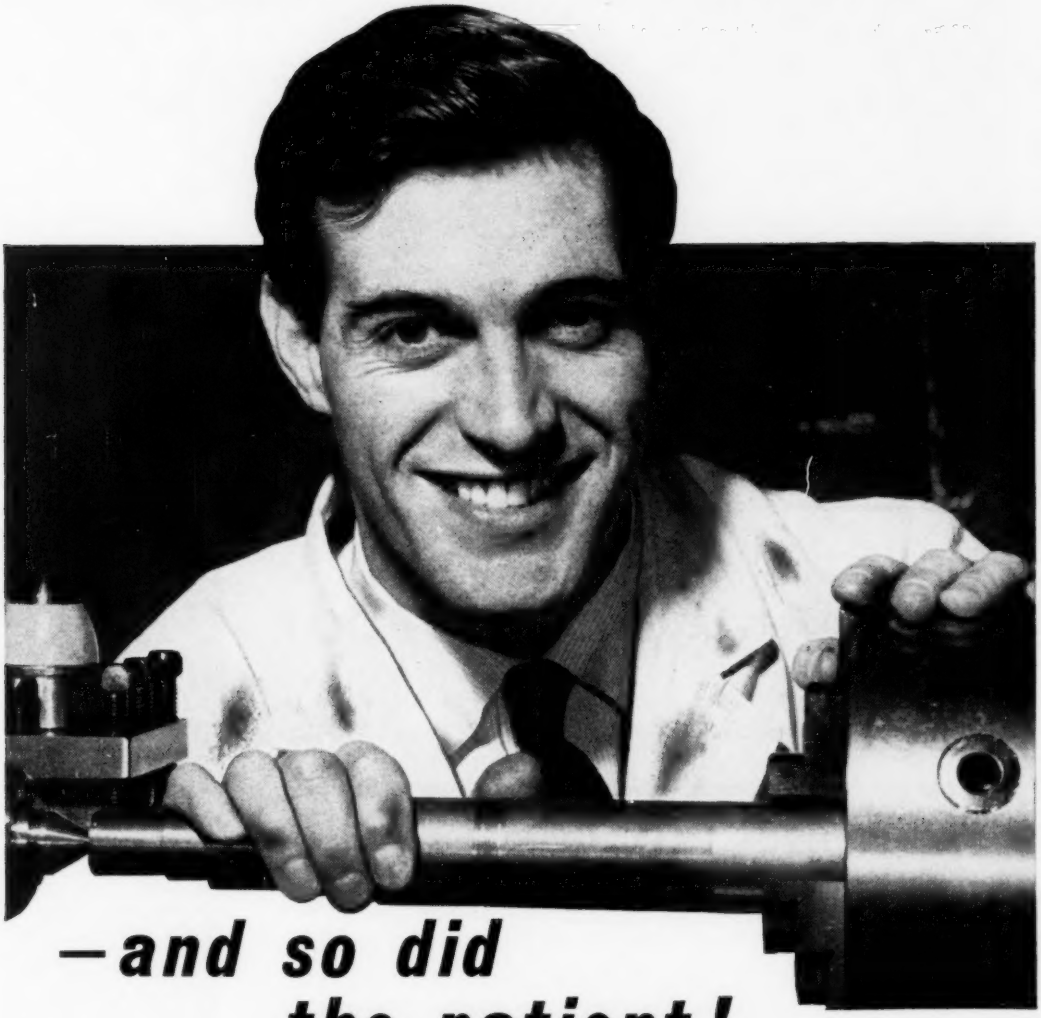
Slough Industrial Health Service, Farnham Road, Slough

Telephone: Slough 22238

ACHROMYCIN* OINTMENT

TETRACYCLINE * REGD. TRADEMARK

soon went to work



—and so did the patient!

Here is an ointment that wastes no time in getting the patient off the sick list. Applied direct to the affected area of the skin, it exerts an immediate and intensive antibacterial action . . . is singularly free from sensitizing effects . . . and can be used time and time again without untoward reactions.

Each gramme contains Tetracycline 30 mg. (3%) Petrolatum-wool fat base.
Packing and basic N.H.S. cost: Tubes of ½ oz. 5/- and 1 oz. 9/2.

Lederle

LEDERLE LABORATORIES
a division of
CYANAMID OF GREAT BRITAIN LTD. London W.C.2

CYANAMID

EAR WAX *Removed this easy way*

LAB

The removal of wax from the external auditory meatus has, in the past, normally entailed attendance by the patient for diagnosis and the application of a loosening agent, followed by a second visit for syringing. With CERUMOL, wax can be removed in most cases at one visit.

CERUMOL is anti-bacterial, non-irritating and harmless to the lining of the external ear or the tympanic membrane.

PACKS for Surgery Use: 10 c.c. vial—separate dropper included (Basic N.H.S. price 2/8); for Hospital Use: 2 oz. and 10 oz. bottles.

Active constituents per 100 c.c.: p-dichlorobenzene B.P.C. 2 gm., Benzocaine B.P. 2 gm., Chlorbutol B.P. 5 gm., Ol. Terebinth B.P. 15 c.c.

CERUMOL
Regd. Trade Mark

Literature and samples for both products gladly sent on request

Prophylaxis of ATHLETE'S FOOT

MONPHYTOL, a volatile, colourless paint, easily applied in a weekly routine, effectively eradicates any dormant fungus and prevents re-infection.

Monilial Paronychia, normally an intractable condition, also responds with immediate symptomatic relief and rapid healing.

Indications

MONILIASIS (Yeasts), Chronic Paronychia*, Intertrigo, Erosio interdigitalis. *See Brit. Med. J. (1955), 2, 1623, for use of Monphytol in this condition.

TINEA (Fungi), Tinea Pedis, Tinea cruris, Tinea circinata, Tinea unguium.

N.H.S. price 3/5 per bottle, bottle, with brush. Prescribable on Form E.C.10.

MONPHYTOL
Regd. Trade Mark

Active constituents per 100 ml Boric Acid B.P. 2 gm.: Chlorbutol B.P. 3 gm.: Methyl Salicylate B.P. 18 c.c.: Salicylic Acid B.P. 12 gm.: Undecylenic Acid B.P. 5.5 c.c.

LAB LABORATORIES FOR APPLIED BIOLOGY LTD.

91, AMHURST PARK, LONDON, N.16 TELEPHONE: STAmford Hill 2252/3

HYDRODERM Regd. ointment

breaks the cycle—
inflammation—itching—infection

Inflammatory skin lesions are often complicated by the presence or threat of bacterial infection. 'Hydroderm' gives simultaneous protection against inflammatory reactions and bacterial infections. 'Hydroderm' combines in an elegant greasy base *Hydrocortisone* and the antibiotics, *Neomycin* and *Bacitracin*. Supplied in tubes of 5 G. and 15 G.

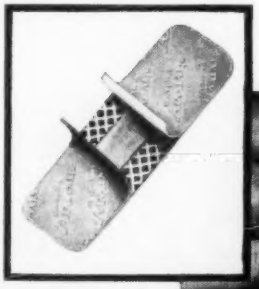
MAIN INDICATIONS FOR 'HYDRODERM': Seborrhoeic dermatitis, Infantile eczema, Adult eczema, Insect bites, Otitis externa, Contact dermatitis, Intertrigo, Pruritus ani, Pruritis vulvae, and similar inflammatory conditions especially when secondary infection is present.

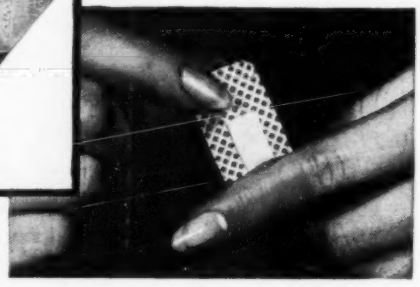
Made in England by
MERCK SHARP & DOHME LIMITED, HODDESDON, HERTS MSD

...nearly 500,000 skin injuries occur each day which require at least a first-aid dressing*

* *Brit Med. J.* 1956. 2. 962.

This suggests that any place such as a hospital or factory where a large number of people are leading active lives, is going to have a fairly high incidence of minor wounds over a period of time. *The most convenient dressing to cope with such injuries is Elastoplast 'Airstrip'.* Elastoplast 'Airstrip' is made from a specially developed plastic material, through which sweat and skin exudates evaporate at the same rate as they develop on the skin. The material is a microporous extensible filter, and is not perforated. It provides a barrier to water, grease and infective organisms. Even after long application, Elastoplast 'Airstrip' does not cause maceration. The surface of the wound and the surrounding skin remain dry beneath an 'Airstrip' dressing, which can be left on until the wound heals.





Elastoplast Airstrip

S&N

SMITH & NEPHEW LIMITED · WELWYN GARDEN CITY · HERTS

Ames

ROUTINE URINE TESTS

—reliable, quick, no external heating—

A **NEW** COLOUR TEST

For **PROTEIN** _____ ***ALBUSTIX**
reagent strips

For **BLOOD** _____ ***OCCULTEST**
reagent tablets

For **GLUCOSE** _____ ***CLINISTIX**
reagent strips

For **BILIRUBIN** _____ ***ICTOTEST**
reagent tablets

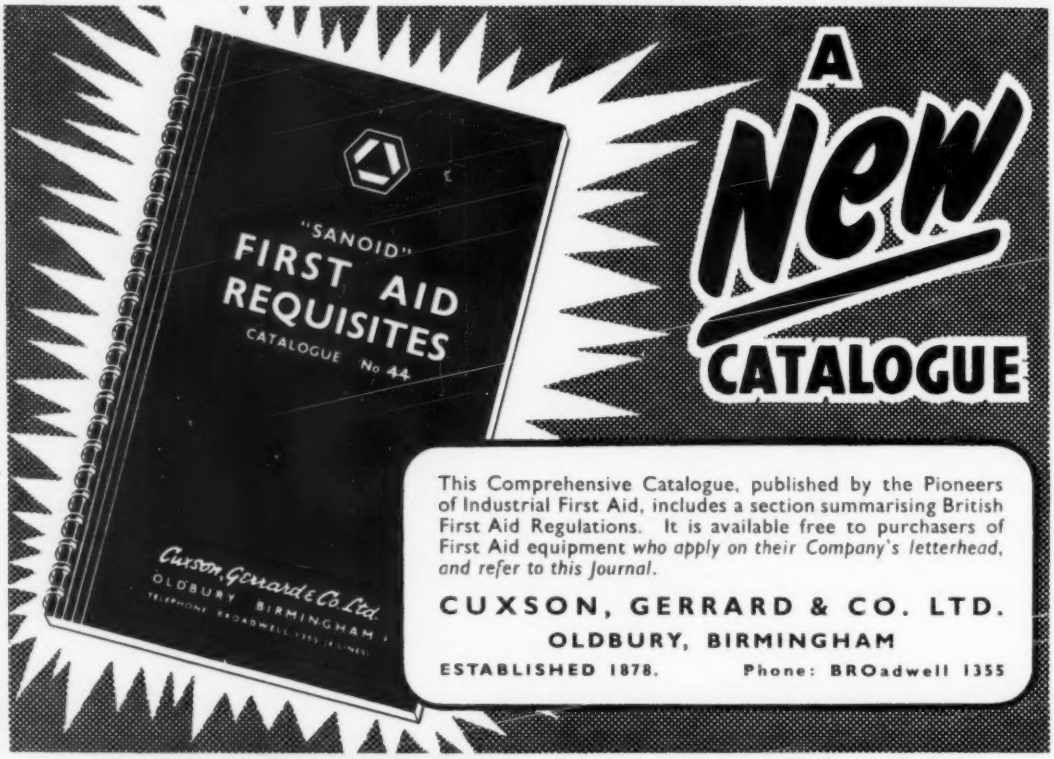
For **KETONES** _____ ***ACETEST**
reagent tablets

. . . and, of course, for reliable estimation of

SUGAR _____ ***CLINITEST**
reagent tablets

Range of six simplified urine tests for General Practitioners, hospitals, clinics and laboratories.
Please write for illustrated leaflet and references.
'Acetest' and 'Clinitest' are available under the N.H.S. on form E.C.10.
(See drug tariff) **Trade Marks*

AMES COMPANY (LONDON) LTD
NUFFIELD HOUSE, PICCADILLY, LONDON, W.1 *Telephone: REGent 5321*


"SANOID"
FIRST AID
REQUISITES
CATALOGUE No 44
Cuxson, Gerrard & Co. Ltd.
OLDBURY BIRMINGHAM
A
New
CATALOGUE
This Comprehensive Catalogue, published by the Pioneers of Industrial First Aid, includes a section summarising British First Aid Regulations. It is available free to purchasers of First Aid equipment who apply on their Company's letterhead, and refer to this Journal.
CUXSON, GERRARD & CO. LTD.
OLDBURY, BIRMINGHAM
ESTABLISHED 1878. Phone: BROadwell 1355

I.C.I. designed this barrier cream specially for industry

Extensively used in I.C.I.'s own factories, I.C.I. Barrier Cream gives better skin protection

* Gives equal protection in wet or dry work.
* Safeguards against industrial dermatitis.
* Protects the hands from staining and ingrained dirt.
* Hands come clean more easily after work.

In containers of 5 lb.

For further information and literature, please write to your nearest I.C.I. Sales Office, or direct to Wilmslow.

I.C.I. BARRIER CREAM

Special rates for bulk contracts

IMPERIAL CHEMICAL INDUSTRIES LIMITED Pharmaceuticals Division Wilmslow Cheshire

ICI

Ph. 914

Brit. J. industr. Med., 1959, **16**, 81.

HEALTH PROBLEMS OF EPOXY RESINS AND AMINE-CURING AGENTS

BY

L. B. BOURNE, F. J. M. MILNER, and K. B. ALBERMAN

From the Cossor Group of Companies and Scientific Pharmacals Ltd.

(RECEIVED FOR PUBLICATION AUGUST 18, 1958)

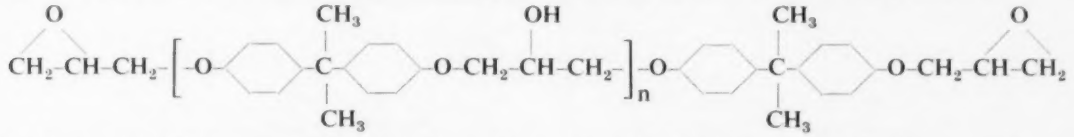
Epoxy resins were first introduced about 10 years ago. Toxic effects, particularly dermatitis, have been frequently described. An investigation into the possible causes of pathological sequelae following the use of epoxy resin/amine mixtures has been undertaken. The cause of most cases of dermatitis and sensitization appears to be uncombined amine which is present in recent mixtures and persists in hardened resin for long periods. The results of experiments with two of the most commonly used resin/amine mixtures confirm this. Cold-cured resins are more dangerous and remain so even when hardened. A simple theory is suggested for the mechanism of the reaction between epoxy resins, amines, and biological systems. This theory leads logically to the handling precautions outlined.

There is a growing literature on the effects of epoxy resins, curing agents, hardeners, and the combinations of these resins with other chemical compounds sufficient to warrant an examination of the possible causes of the difficulties which have resulted from the manufacture and use of these substances. These resins were first introduced into England about 10 years ago from Switzerland. As originally conceived in 1936 the resins were an attempt to produce a compound capable of being used in a mould for dental work without shrinking when polymerized. According to Narracott (1953), I. G. Farbenindustrie first disclosed that epoxy resins with the addition of amines could form hardenable products satisfactory for cementing and bonding. Soon after this, Custans in Switzerland found that amines could cure epoxy resins and the CIBA Company have widely patented this method. Most of the hazards may be avoided by good engineering installations and " no touch " technique but these are not always applicable in the wide field of use and also depend to a large extent on the quantities of raw materials used.

Little is known of the systemic effects in man of many of the newer chemicals used in these processes, as much experimental work is being carried out with modified systems and new materials. There are few reports of preliminary work on the toxicity of the chemicals, and furthermore the position is complicated by international patent problems which have encouraged some manufacturers of the primary materials to be reticent about giving this information.

Chemistry of the Epoxy Resins

Essentially the epoxy resins fall into the category of thermo-setting materials, although, in many cases, the system employed may be classified as " cold curing ". This is meant to indicate the absence of applied heat rather than the absence of heat altogether as in all these systems heat is generated in the chemical reactions which occur. Epoxy resins are the reaction product of two chemicals, epichlorohydrin and diphenylolpropane. This is a condensation reaction which results in long chains which have the generalized formula:



In this formula " n " indicates a number of repeated units of the form contained in the bracket.

The epoxy group is the group which is present at both ends of the chain and it is through

this and the pendant hydroxyl, —OH, groups that reaction occurs. Both these groups are chemically reactive, a fact which is of importance when considering the physiological properties of the resins themselves. The activity is, however, of a low order and the resins are stable to a large extent, indicating that there is little interaction of the epoxy and hydroxyl groups. There are a number of possible variations of this product, each designed to impart improved properties in one or more directions, but the generalized form is sufficient for this discussion. These forms vary from fairly low viscosity liquids to fusible solids and may contain additions such as solvents or plasticizers. They are readily attacked by chemicals and are readily soluble in a variety of solvents.

The low viscosity resins are composed of short chains, *i.e.*, " n " in the above formula is comparatively small. It will be evident, however, that this type of resin will have more epoxy groups since every chain has one at each end. The more viscous or solid resins have longer chains and correspondingly fewer free epoxy groups are present. This will have a bearing on the physiological properties from two aspects. First, the less viscous resins are more readily miscible with or soluble in other liquids, which may include such physiological fluids as sweat. Secondly, if there is any medical objection to the epoxy group this will be more pertinent in the case of the low molecular weight resins than the higher.

Further, the passage of a low molecular weight or short-chain polymer through a permeable or semi-permeable membrane will be easier than with the longer chains. This applies also in the case of the curing agents discussed below. It should be noted however, that low viscosity in an epoxy resin may not be inherent in the resin itself but may be due to the presence of a solvent or plasticizer.*

In all cases these resins are converted to hard, infusible solids by the addition of certain substances which are generally termed " curing " agents or hardeners. Some curing agents will react without the addition of heat and are designated as " cold " curing while others require the application of external heat and are designated as " hot curing ".

In the case of cold-curing reactions, although an infusible solid can be produced without heat, the best properties of the resin system are usually developed by applying heat to the cured material, a process which is generally referred to as " post curing ".

Curing of the epoxy resin is brought about by a chemical splitting of the epoxy ring which leads to linkages between the long-chain molecules. This linking takes place in such a way that a three-dimensional lattice is built up which is chemically very stable and unreactive and which has excellent electrical and mechanical properties. The cured resins are extremely resistant to all solvents. These properties have led to the widespread use of these resins for adhesives, laminating, embedding or potting of electronic circuits, and in paint formulations. They are now also being used quite widely in the manufacture of tools and, for example, press tools. The final properties of the cured system depend to a large extent on the curing agent used and the method of cure. The resin worker is influenced more by process and product considerations in his choice of system than by medical considerations.

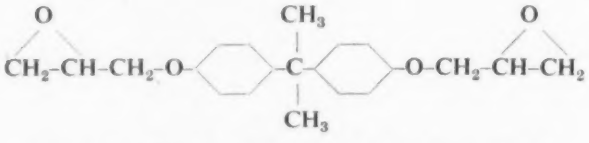
The classification of curing agents as hot or cold curing is of value practically, but medically the chemical classification of the materials is more important and it is in this way that we shall consider them. The most commonly used curing agents belong to the class of chemicals known as amines, and next to these in use are the acids and acid anhydrides. Chemical variants of these two groups are becoming prominent due to efforts within industry to produce safer handling materials but the reactivity of these materials still rests in the same functional chemical group. One other group of materials is rapidly gaining wide acceptance on account of their many advantages as curing agents, coupled with their relatively much safer handling. These are the polyamides. Each of these groups will be considered separately.

Amines.—Amines fall into three groups and have the following generalized formulae:—

Primary amine . .	. .	RNH_2
Secondary amine	. .	R_2NH
Tertiary amines	. .	R_3N

" R " in these formulae represents any organic group, which may be a straight chain, in which case the amine is referred to as aliphatic, or it may be a ring compound, in which case the amine is referred to as aromatic. Aliphatic and aromatic amines of all

* Chemically the epoxy resins are homologues of the diglycidyl ether of diphenylolpropane



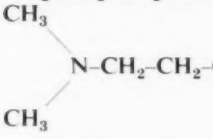
which, it can be seen, has the generalized formula given earlier, " n " here being O. The commercial resins contain proportions of this and other straight chains with varying values of " n " as well as some branched chain molecules. The simple diglycidyl ether, however, is representative of the epoxy structure and for this reason has been used in some medical studies on the epoxy resins (Hine, Kodama, Wellington, Dunlop, and Anderson, 1956).

Ethylene diamine .. .. $NH_2–CH_2–CH_2–NH_2$ .. .. primary aliphatic

Diethylene triamine .. .. $NH_2–CH_2–CH_2–NH–CH_2–CH_2–NH_2$ .. .. ,, ,,

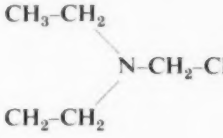
Triethylene tetramine .. .. $NH_2–CH_2–CH_2–NH–CH_2–CH_2–NH–CH_2–CH_2–NH_2$,, ,,

Dimethylamino propylamine ..



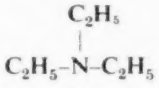
,, ,,

Diethylamino propylamine ..



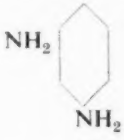
,, ,,

Triethylamine .. .. ..



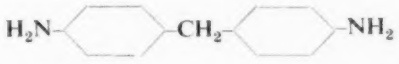
.. .. tertiary aliphatic

Metaphenylene diamine ..

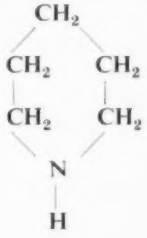


.. .. primary aromatic

4_14 Methylene dianiline ..



Piperidine .. .. ..



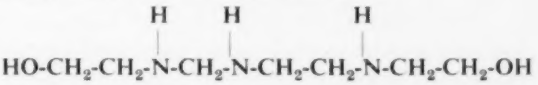
types can be used as curing agents for epoxy resins. The most commonly used are listed above.

It should be noted that with the exception of piperidine these compounds contain two or more amine groups and are usually referred to as " polyamines ".

This list is by no means exhaustive and takes no account of the many variants based on these and other amines which are also available. The amines are, for the most part liquid, although some are solid, *e.g.*, metaphenylene diamine, as is also the case with some of the chemical variants available. In the case of these solid materials, however, they are either brought to a liquid state by heating for incorporation into the resin, or alternatively they are dissolved into the hot resin. It should also be noted in this respect that solid resins have to be brought to the liquid state by heating for incorporation of the curing agent.

The liquid amines in the main are highly volatile, pungent materials which may fume profusely in the air and are soluble in water. They are strongly alkaline and highly reactive and all have physiological hazards. Certain of the modified amines or amine adducts, *e.g.*, amine oxide type adducts which are of use in the adhesive and laminating fields, are claimed to be less irritating than the normal amines and for this reason have been designated as having "minimum irritation potential" or M.I.P. It must be stressed, however, that these materials are still essentially amine in character, *e.g.* :

Bis-hydroxy ethyl diethylene triamine



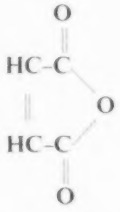
Organic Acids and Acid Anhydrides.—Organic acids have not found much use as curing agents for epoxy resins but may be employed and are best

evidenced by oxalic acid, the toxicity of which is well known.

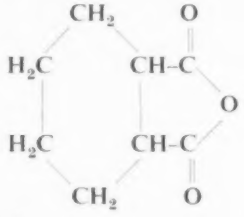
Acid anhydrides, on the other hand, have found fairly wide acceptance.

The most popular of these is phthalic anhydride which has the formula:—

Other anhydrides give similar reactions, and maleic anhydride



and hexahydrophthalic anhydride



have been used.

These acid anhydrides are solids which readily react with water to produce the corresponding acid. Other liquid anhydrides and liquid anhydride adducts can also be used. Some of these materials are known skin irritants and as all react with moisture to produce organic acids of varying strength, care in handling is definitely indicated. Further, to improve their properties as curing agents small percentages of amine curing agents may be incorporated.

In all cases these materials act as hot-curing agents and with the solid materials heat is necessary to effect solution in the resin.

Polyamides.—Polyamide resins form a particular class of curing agents. They have gained acceptance primarily as modifiers for the epoxy system to impart flexibility and improved impact resistance but are peculiar in that they can also cure the epoxy resin. Polyamides are the condensation products of dibasic acids and diamines and the best known products of this reaction are the " nylon " series of plastics. The polyamides used for curing epoxy resins are, however, a specialized group with different properties from the " nylons ". These materials are very complex chemically but owe their activity to the amine group in the molecule. Generally, these materials are viscous amber liquids. They can be used as cold- or hot-curing agents and have the added merit of cold-curing with low exotherm.

As a class these resins are probably the safest. They are not known as irritants and their ability to cold-cure with low exotherm excludes the hazards which result from the effect of heat on the other curing agents. One word of warning must be given here, however. Their high viscosity and their relatively slow rate of cure have led to modifiers being introduced to lower the viscosity and speed up the cure. These modifiers may be amines or amine adducts which may or may not fall within the category of M.I.P. curing agents. The comparative safety of the polyamide may be lost in this way.

Other Curing Agents.—Some other curing agents may be employed but these are not in general use. One of these is boron trifluoride amine complex. This material is used to produce high heat-resistant products but requires high temperature curing and at these temperatures produces toxic vapours.

Phenolic materials, especially amine phenolic derivatives such as dimethyl amino methyl phenol and its salts, are also used. Each of these compounds has to be considered individually in its physiological reactions but the acid salts of the amino phenolics are claimed to have low toxicity.

In order to bring about cure in an epoxy system the appropriate amount of curing agent must be brought into intimate contact with the epoxy resin. Chemical reactions can be postulated for the mechanism of curing and on the basis of these the amount of curing agent appropriate to a given amount of epoxy resin can be calculated. Ideally the reactive curing groups should be equal in number to the reactive groups in the epoxy resin. For various reasons which are beyond the scope of this article, this is not possible and approximations have to be made which in practice produce the desired results. As a result it is possible to have unreacted reactive groups, either epoxy or curing, in the cured system and this fact will be referred to later.

In practice the requisite amounts of resin and hardener are weighed into suitable containers. Either or both may then be heated to facilitate mixing, which may be carried out by hand or

mechanically. In the case of liquid hardeners, the volume corresponding to the weight may be calculated and measured out using volumetric equipment such as a tilt measure which can be preset to deliver a given volume. During all these operations the operator can be exposed to physical contact with both resin and curing agent and also to any vapours arising from them.

After mixing, the resin system is used in various ways. As an adhesive the mixed resin is applied to the surfaces being bonded, an operation which can involve considerable danger to the hands. In laminating the resin may be smeared over a moulding between layers of the appropriate laminating material. This is one of the most dangerous operations for contaminating the hands and it is perhaps fortunate that the high price of epoxy resins, among other things, has prevented their wide adoption for this type of work. In potting work the mixed resin is poured into a mould, usually metal but sometimes polythene or other suitable plastic, which may have been previously heated. With reasonable care, the hands need not be in contact in this operation, but there is considerable danger from vapour, especially using hot systems.

In all these applications the system may be hot- or cold-cured. Laminating systems are normally cold-cured, but if heat is required it is normally applied by means of heaters built into the mould. Pressure may be used in this case also, and this may be applied by means of a vacuum bag technique. In this case any vapour coming from the system will be sucked off through the vacuum pump and may be discharged at a point quite remote from the mould. Adhesive and casting systems are also hot- or cold-cured. For cold-curing the system is simply left aside for the appropriate time for curing to take place. Hot-curing in both cases is normally carried out in an oven. In this case, unless the oven is fitted with efficient extraction, there may be a considerable concentration of volatile fumes in the oven. Operators opening such ovens will be exposed to these hot vapours. It is important that extracted fumes from curing ovens are discharged clear of any employees.

When cure is complete the product is removed from the oven and/or the mould. At this stage the system is handled. This should be a safe procedure, but in certain cold systems a film of unreacted curing agent may be present on the surface when it comes in contact with the air. Further, cured systems may be subjected to machining, an operation which is generally regarded as safe, but in view of the possibility of unreacted curing agent being still present, this is open to question and will be discussed again later.

On the chemical side it should be noted also that many modifying agents such as fillers and plasticizers may be incorporated into the resin system, particularly in casting and laminating work. Some of these, such as mica, silica flour, and fibreglass materials, may have health hazards in themselves, to which appropriate attention should be given.

One last application which has not been discussed above is the use of epoxy resins in paints. So far no serious trouble has been encountered in this field, probably due to the low reactivity of the hardeners employed, but care should be exercised since essentially chemically active substances are involved, and in application these are present in solvents which may readily penetrate the skin, carrying resin and curing agent with them. A recent addition to this group is a pitch-epoxy resin surface coating which, it is claimed, is cold cured with normal amine curing agents. A solution of diethylene triamine in secondary butanol is claimed to give good results. This system is being recommended for brush or spray application to such items as pipes and tanks. As the amine hardeners are known as a serious dermatitis risk, and in this case they are present in a volatile solvent, extensive precautionary measures will undoubtedly be necessary, particularly with spray applications.

Experimental

It was decided to investigate the possible cause of dermatitis in the more commonly used mixtures particularly with regard to the amounts of amine used, as all suppliers recommend the provision of larger amounts of these than appears absolutely necessary to harden the resin. As one of the commonly used resins contains an unspecified plasticizer, this may have been of considerable influence in increasing the risk. It is also generally accepted that some of the many by-products which may result from these combinations may be the cause of some cases of dermatitis, but from previous experience it was likely that unused amine could be the most potent hazard.

Resin triethylene tetramine (" D "/T.E.T.) mixtures were prepared under normal factory conditions. These were then de-aerated until no bubbles were seen to emerge from the mixtures. Small amounts were then spread on microscope slides. The *p*H of these mixes is about 10 to 11. Some of the slides were allowed to harden in air, others were placed in ovens at 60°C. It was found that all air-dried mixtures were of ground-glass appearance whereas those stoved were much clearer, some being transparent. On microscopic examination the ground-glass appearance (Fig. 1) was due to circular bubbles of two types, some appearing to have a denser opaque centre and others fairly clear as if gaseous (Fig. 2). As resin D is known to contain a plasticizer (possibly di-octylphthalate), resin from another supplier containing no plasticizer was mixed with T.E.T. and examined after stoving; the result was a film

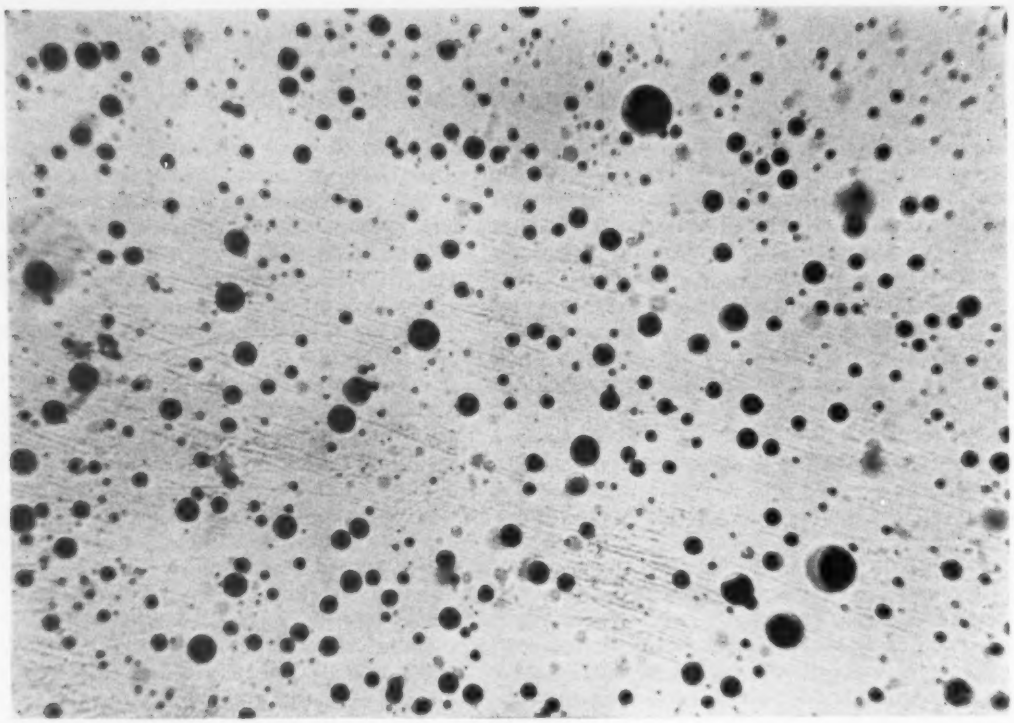


FIG. 1

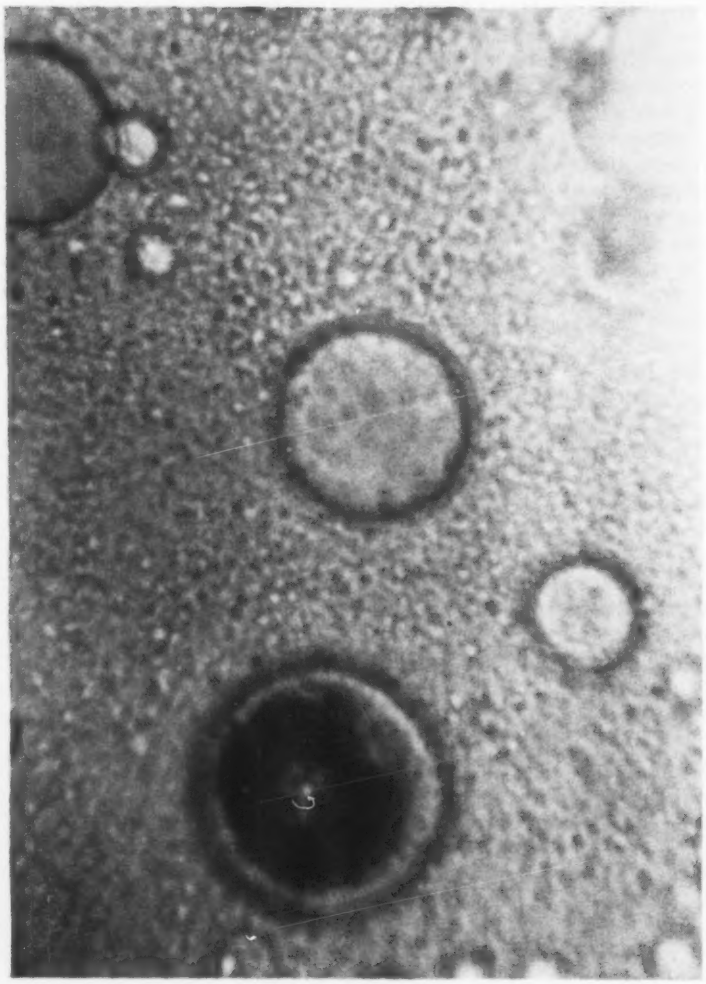


FIG. 2

FIG. 3

FIG. 1.—Resin "D"/T.E.T. mixture to suppliers' recommendation. Air cured. Unstained. × 120.

FIG. 2.—The same film. × 720.

FIG. 3.—Resin 828/T.E.T. mixture to suppliers' recommendation. Oven cured. Unstained. × 120.

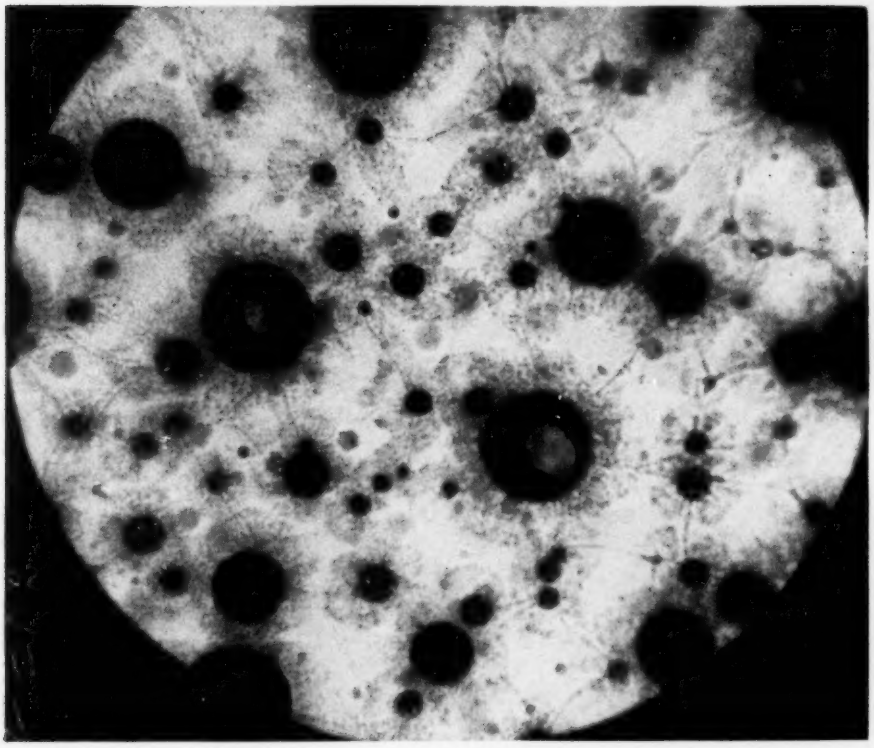


Fig. 4.—Resin " D "/T.E.T. to suppliers' recommendation. Stained MEK/Leishman. × 300.

surprisingly free from bubbles, in fact, only one was found with difficulty (Fig. 3).

A simple technique for identification of the bubbles was desirable. Highly technical methods such as microscopic spectroscopy were not available. Biological staining technique offered a possibility if the resin films could be softened enough to permit staining. Methyl ethyl ketone (MEK) to which eosin acid (E. Gurr) was added to give a *p*H of 4 was found to be satisfactory. A film of " D "/T.E.T. was covered with the staining solution for 24 hours and it was found to be hard and had become stained red. Staining with a basic (MEK + methylene blue + KOH, *p*H 11) stain had no effect but an MEK/Leishman stain on a similar film gave a surprising result with only the acid stain being absorbed (Fig. 4). The results reveal that the films stain readily with acid stains. As hardened films of all resins with T.E.T. hardener, when tested with wet universal indicator papers gave a *p*H of at least 9, it was decided to test mixtures under varying conditions with the results set out in Table 1.

All mixtures were de-aerated and allowed to stand for three days after hardening.

All air-cured materials gave a mottled ground-glass appearance. These were retested one week later with similar results.

As the high *p*H of the hardened resins may have been due to excess amounts of amine hardener, mixtures were prepared containing both less and more than the suppliers' specification. If a true chemical combination took place then small amounts of amine were likely to be absorbed in the reaction. Twelve specimens were prepared as in Table 2.

TABLE 1

RESULTS WITH 828/T.E.T. MIXTURE

Mixture No.	Condition	*p*H
1	Room air cure	10
2	Dry air cure (in dessicator)	10
3	Moist air cure (rel. humidity 100%)	11
4	Oven cure	8

TABLE 2

COMPOSITION OF 12 SPECIMENS OF RESIN " D " AND T.E.T.

Mixture No.	Resin " D " (parts)	T.E.T. (parts)
1a	24	3
2a	27	3
3a	30	3
4a	33	3
5a	36	3
6a	42	3

These specimens were mixed in air, de-aerated, and cured in dust-free air.

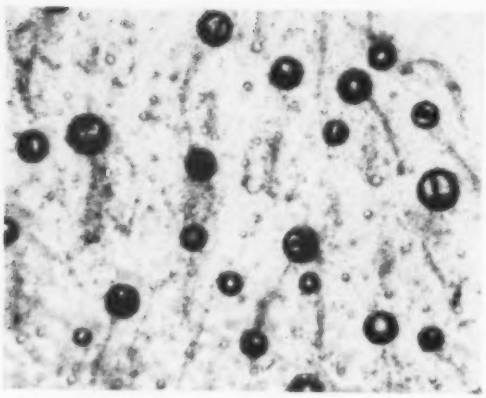


FIG. 5.—Mixture 1a.

FIG. 6.—Mixture 1b.

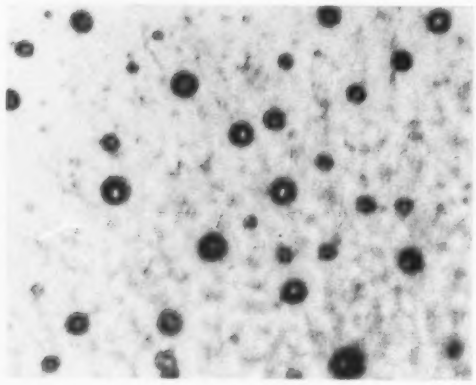


FIG. 7.—Mixture 2a.

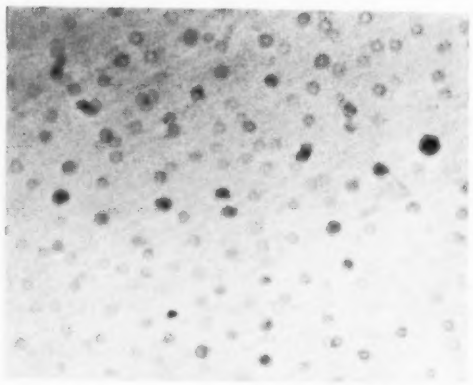


FIG. 8.—Mixture 2b.

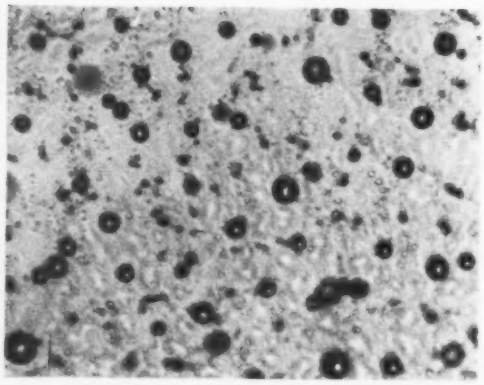


FIG. 9.—Mixture 3a.

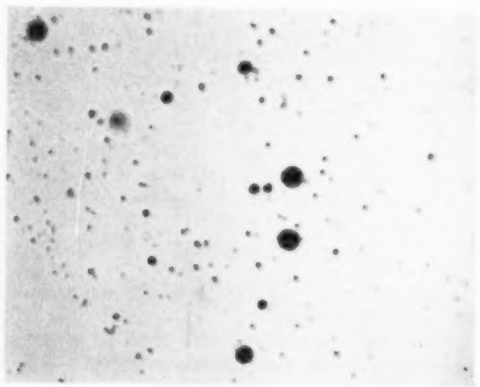


FIG. 10.—Mixture 3b.

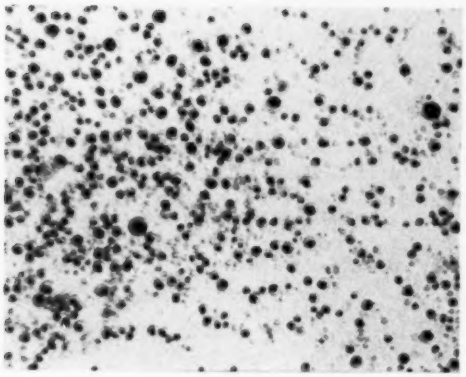


FIG. 11.—Mixture 4a.

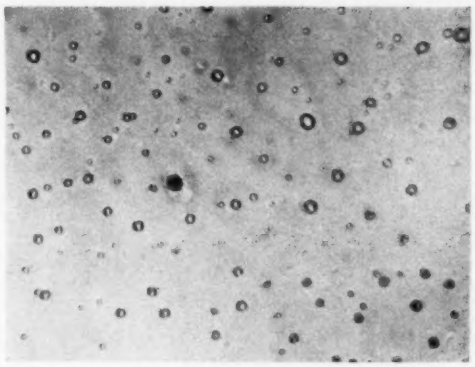


FIG. 12.—Mixture 4b.

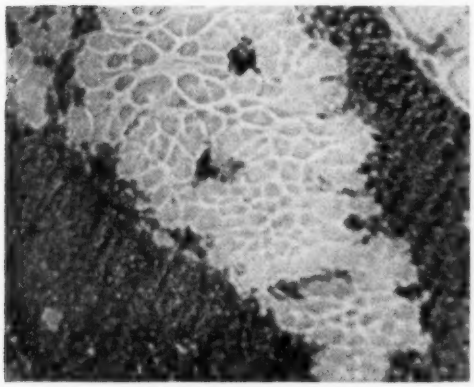


FIG. 13.—Mixture 5a.

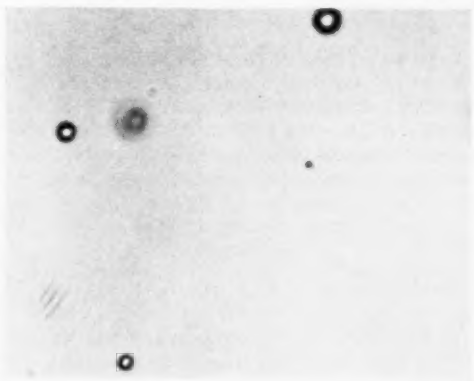


FIG. 14.—Mixture 5b.

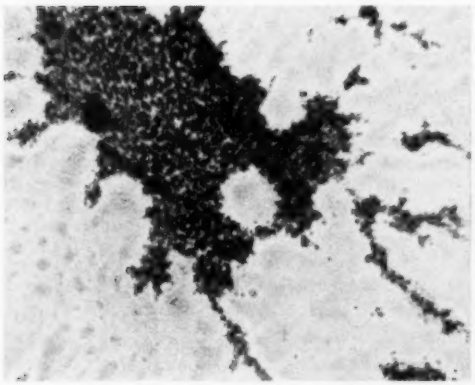


FIG. 15.—Mixture 6a.

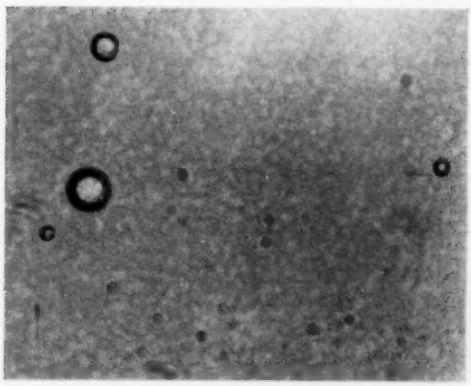


FIG. 16.—Mixture 6b.

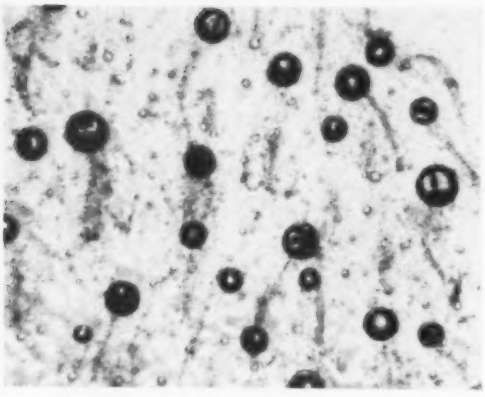


FIG. 5.—Mixture 1a.

FIG. 6.—Mixture 1b.

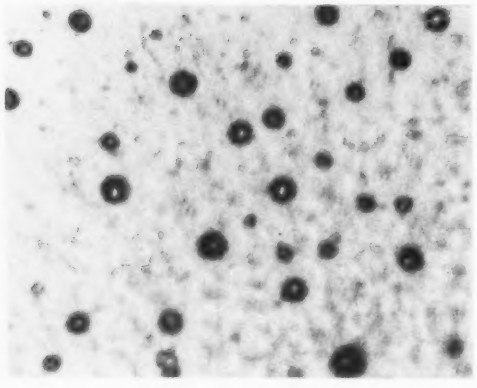


FIG. 7.—Mixture 2a.

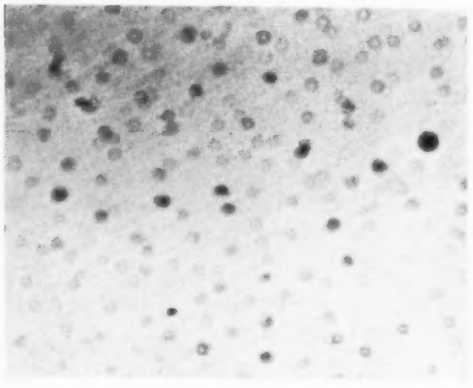


FIG. 8.—Mixture 2b.

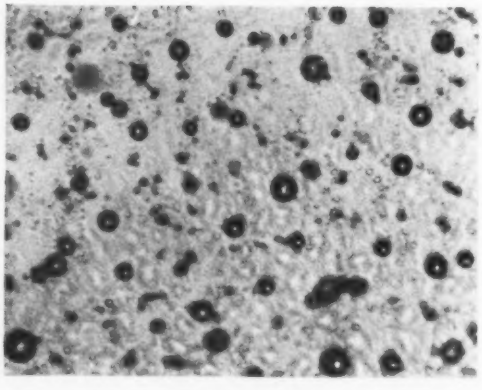


FIG. 9.—Mixture 3a.

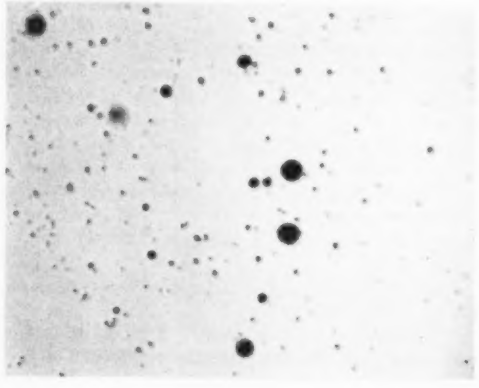


FIG. 10.—Mixture 3b.

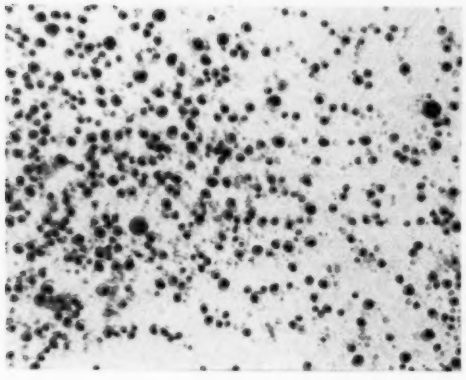


FIG. 11.—Mixture 4a.

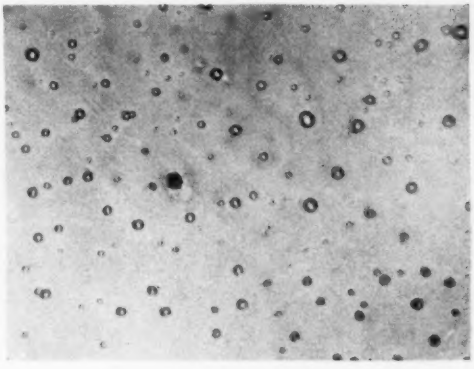


FIG. 12.—Mixture 4b.

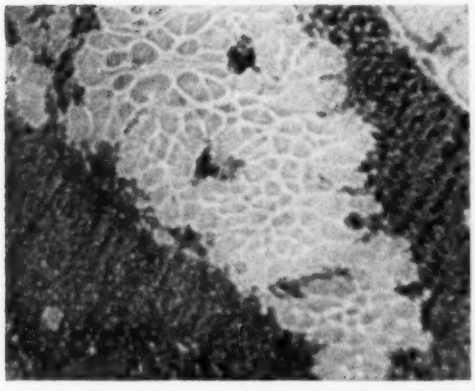


FIG. 13.—Mixture 5a.

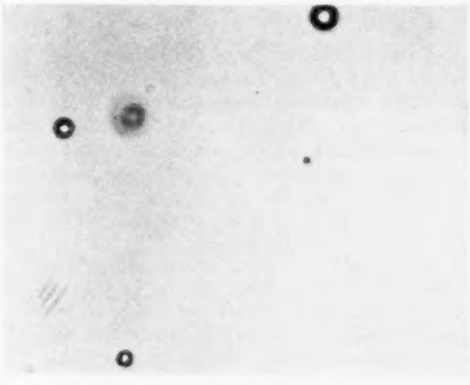


FIG. 14.—Mixture 5b.

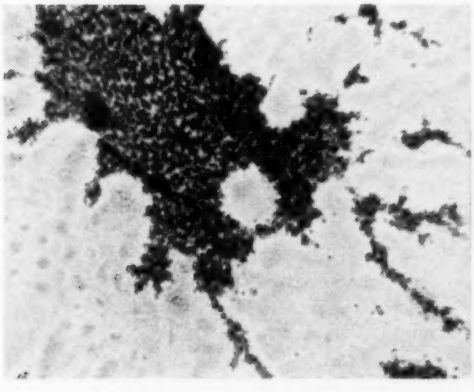


FIG. 15.—Mixture 6a.

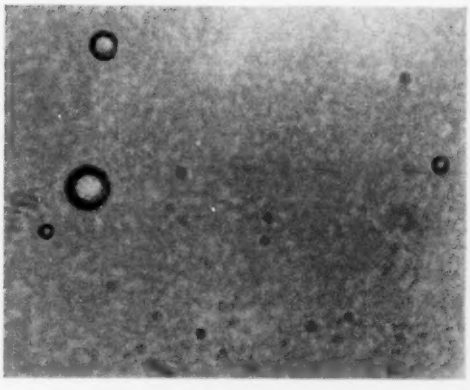


FIG. 16.—Mixture 6b.

FIG. 17.—Greasy and finely pitted air-free surface of moulded block of " D "/T.E.T.

A similar set (mixtures 1b to 6b) in the same proportions was prepared by 15 minutes' exposure to air, de-aeration, followed by cure at 60°C. for one hour (1b to 6b). The only variant was the time between weighing and mixing.

In accordance with our previous findings, all air-cured specimens gave a mottled appearance and oven-cured specimens were clear. On microscopic examination in all cases bubbles were visible, but much reduced in the stoved specimens. It was also noticeable that as the amount of amine is reduced there were fewer bubbles visible (Figs. 14 to 16).

A further common finding is that when blocks of resin are formed in moulds, the air-free surface is found to be greasy and finely pitted (Fig. 17). The *p*H of this damp surface is about 12. The other surfaces of the moulded piece are dry and smooth.

As many of the mixtures include fillers such as mica dust or chalk, specimens of these mixtures were tested; they did not show bubbles although there were similar alkaline reactions at the air surface as noted above.

After six months the original cold-cured slides of resin-amine mixtures were again tested for alkalinity and in all cases a *p*H of 10+ was demonstrated.

A cast block of " D "/T.E.T. resin in the proportion of 10/1 at least a year old was ground to powder and tested with hot extraction by acetone and water with the following results:

RESIN SYSTEM D/T.E.T.

Hot Extractions	
(i) Acetone	14·9% loss in weight
(ii) Water	2·46% loss in weight
Acetone Extract	
Nitrogen content = 0·04%	
= 0·1% triethylene tetramine	
Aqueous Extract	
Equivalent to 0·6 ml. N/10 HCL/g	
or 0·078% nitrogen	
or 0·2% triethylene tetramine	

Conclusions.—The higher acetone extract is to be expected since it would contain low molecular weight polymers, unreacted resin, unreacted hardener, and plasticizer; whereas the water extract would leach out unreacted hardener and possibly only traces of the plasticizer and resin, together with water-soluble impurities of these.

Estimation of alkalinity on the aqueous extract and of nitrogen on the acetone extract indicated a free hardener content throughout the body of the cast resin of from 0·1 to 0·2% free amine.

Using a resin-hardener ratio of 10:1 this means that possibly 1% of the added amine remained in the body of the resin in the unreacted state.

Physiological Effects

Reports of the toxic effects on the alimentary canal tend to show that the risks of absorption here are small. It is of interest to note that these resins when fully polymerized have been used to coat the inside of food containers for some years without apparent harm to consumers.

Shell Chemicals Limited (1954) report that starved white mice were given epoxy resin 75% and 50% in dioctyl phthalate by the intragastric route in a syringe, first at room temperature in doses from 3·2 ml./kg. to 7·1 ml./kg. and then at 37°C. in doses from 13 ml./kg. to 30 ml./kg. without ill effect. In a further experiment to test subacute toxicity, the same mixtures and an epoxy resin 100% were added to the diets of male rats for 26 weeks and no gross or histological abnormality was seen in liver, lung, heart, kidney, stomach, intestine, or bladder. The only positive finding was that the ingestion of resin amounting to 1% of the diet caused a weight loss.

Hine *et al.* (1956), in a series of animal experiments to test the effects of epoxy resins, administered glycidol and five related ethers to animals and found that in addition to other systemic effects, the central nervous system was depressed on intragastric administration.

Bakelite Limited (1957) have issued the following report of work done at the Mellon Institute, Pittsburg:—

> " A summary of our laboratory results with ZZLB-0814 hardener is as follows. When administered to rats by mouth, this product has an LD_{50} dose of 5·6 grams per kilogram body weight. As a matter of interest this is in the same general quantitative range of oral toxicity for the rat as lactic acid, n-hexanol or oil of citronella."

Another American Company, General Mills (1957), state that their " polyamide catalyst (' versamid 125 ') was fed to albino rats and that the acute oral mean lethal dose (LD_{50}) is greater than 8·0 g./kg. This material is relatively non-toxic by the oral route ". They also state that this com-

pound is not a sensitizing agent in the albino guinea-pig and that " these materials can be considered to be practically non-toxic by the percutaneous route. A mild erythema is produced at the exposure site, but no signs of systemic toxicity are manifest ".

Pyridine is certainly toxic and is considered by some authorities to cause severe liver and kidney damage in addition to other pathological effects (Browning, 1953). There is unlikely to be much risk of direct ingestion of these materials during work, and, in view of the evidence quoted, accidental ingestion should not result in toxic sequelae.*

A much greater hazard results from exposure to volatile curing agents. Pyridine if inhaled has an irritant effect on mucous membranes, the respiratory tract, and conjunctivae (Jacobs, 1941). Piperidine (hexahydropyridine) is suspect, as the *British Pharmacopoeia* notes that it has a coniine-like action. Aniline formaldehyde (A.F.) resins added to epoxy resins give useful commercial products but the mixing of the two compounds may possibly produce an irritant vapour as the required temperature for reaction is 100 to 120° C. when the A.F. resin is stirred into the hot epoxy resin.

Of all the curing agents T.E.T. is the one which has been found to cause most trouble. Grandjean (1957) tested the concentration of T.E.T. at head level at room temperature in a factory where epoxy/T.E.T. mixtures were being used throughout the day and found that " at a normal work bench the average concentration of T.E.T. vapour at head level is below the limit of measurement of 0·15 μg./l. air ". This may be true of the conditions examined by Grandjean, but where relatively large amounts of these materials are used such as in castings up to half a ton, an experienced authority (Pentz, 1957) has expressed the opinion that " in our experience a considerable part of the dermatitis that has arisen has in fact been caused rather by vapour than by liquid contact and, further, the liquid epoxide resins, though less troublesome than liquid amine hardeners, are themselves not to be regarded as innocuous ".

A common symptom is erythema of the face with oedema of the peri-orbital regions and marked pruritus resulting from hot vapour escaping from ovens in which trays of small parts treated with resin are being baked. The operator usually places trays of work in these ovens without taking precautions to guard the face. Indirect exposure to the vapour as a result of convection currents at a distance from the actual process has caused many cases. If the vapour is inspired attacks of coughing develop which may be followed by temporary respiratory distress but no permanent damage to the respiratory tract results. Intermittent exposure causes a return of the symptoms which, in most cases, subside when the sufferer ceases work, and there is usually no discomfort by next morning. Dernehl (1951) noted an allergic effect on the respiratory tract from ethylene amines but Savitt (1955) was not able to corroborate these findings as to the asthma-like reactions after continuous exposure with similar amines. We have not met any cases presenting asthmatic symptoms but, by analogy with other volatile chemicals, asthma would appear likely to develop in susceptible subjects. We have not seen any lesions of the nasal or buccal mucous membranes.

The results of skin contact have given the most trouble and the first symptoms, whether caused by vapour or direct primary contact from the resin or curing agent mixture or the curing agent alone, are similar to those of most volatile industrial irritants. Physiological activity appears to have a direct relationship with physical and chemical activity. From the hot vapour as previously noted, there is marked pruritus and erythema and oedema. The first effect may be immediate or delayed for some days. This may settle down and clear, but on return to exposure the reaction is likely to recur in most people, usually within hours or days and be more severe causing a generalized erythema with oedema of the face, particularly of the peri-orbital regions, and also a marked conjunctivitis. Excoriations of the backs of the hands are commonly seen. In other cases where there is a history of splashes, vesicles or bullae may form, or a punctate erythema may develop with marked folliculitis to be followed by an exfoliative dermatitis.

Resin or amine contamination in the nail regions may result in paronychia. Splashes harden on the skin and physical removal often causes trauma to the keratin. Care must be taken not to transfer any contaminant to unprotected areas of the body, as in a case previously described (Bourne, 1957), in which a man although fully protected with barrier cream on the hands and with no record of symptoms, left his work place to urinate without washing his hands and conveyed some of the mixture to his penis with unfortunate results. A similar case has recently been seen in an unprotected research chemist.

Perspiration increases the risk and is likely to intensify the symptoms. Dernehl (1951) in his series found that 80% of all personnel at risk reported dermatitis within three years and most cases (66%) occurred in the hot months. He was of the opinion that both irritative and allergic phenomena are active.

* Pletscher and his colleagues (1954) reported signs of functional disorder of the liver, which they attributed to the action of hardeners, but this result has not been confirmed elsewhere.

Savitt (1955) painted undiluted amine on the skin of the belly of rabbits and reported " severe corrosive reaction with toxic effect ". When he diluted the amine to 10% in water, the skin reaction was eliminated. This does not appear to be a satisfactory criterion as the amines are used undiluted in industry.

As previously pointed out, the reaction between an epoxy resin and curing agent is exothermic and may be considerable, as much as 60 calories per gram being generated, but in common with other observers we have not as yet noted any skin burns from this.

In general the amines may be classified as direct primary irritants and also may act as secondary sensitizers. Cross sensitization with other amines has been noted in laboratory workers where short-term exposures to many amines are usual and also in factories where a process has been changed. It is generally held that the epoxy resins are less liable to cause skin reactions, but Hine and his colleagues (Hine *et al.*, 1956) found that glycidol and the glycidyl ethers cause irritation of the skin ranging from erythema to eschar on cutaneous application, but all produced some irritation.

Attention has been drawn to the greasy pitted appearance of the air-free surface of moulded blocks of resin and its high *p*H. This film disappears when the surface is subjected to heat but returns when the resin recools and eventually may disappear altogether on repeated heating. This surface effect may well have been the cause of dermatitis in a patient with a prosthesis made of a resin-amine mixture.

A man with a partially amputated arm was fitted with a prosthesis made of epoxy resin-amine lamination. A few days after, a severe dermatitis developed in the stump, significantly in an area where some patching with resin had been carried out after the original casting. The prosthesis was then restoved for three days at 80°C. and was reapplied to the limb after the dermatitis had cleared. No further skin reaction was experienced. The exudate of high *p*H material may well have been the cause of dermatitis in this case.

The working of the finished resin product does cause serious problems, particularly where employees have become sensitized. The fine dust which arises when laminates or castings are machined, drilled, sandpapered, or filed causes marked irritation or erythema of the mucous membranes and skin in spite of the opinions expressed by the suppliers of the raw materials that the so-called polymerized epoxy resin is safe.

A research engineer contracted dermatitis in developing new combinations of epoxy-amines, became generally sensitized, and is now highly reactive to minute quantities in the atmosphere of any part of the resin mixture in any stage, cured or uncured, and if he enters a laboratory or shop where the finished product has been worked he flares up in under a minute. At one period he developed an acute psychosis as a result of the pruritus and had to be treated in a psychiatric hospital.

A manufacturer of sports equipment purchased rod sheet and fibre glass laminates of epoxy resin for use in making tennis racquet frames, golf club handles, etc. During the machining and working of this material, cases of dermatitis developed in practically all those at risk as a result of the powder given off by the material.

Phenylene diamines have been recommended, particularly metaphenylene diamine, which is used where special heat-resisting polymers are required. In this process the meta-phenylene diamine in powder is heated until it is molten and then mixed with the resin. The whole operation should be carried out in a fume cupboard, as the meta-phenylene diamine sublimes, contaminates the atmosphere, and settles on neighbouring objects and eventually causes brown staining of the skin but no irritation. It should be noted that the phenylene diamines, toluene diamines, and other alkylated benzene diamines and the salts of these compounds are included in the schedules of the Poisons List (1949) and the Poison Rules (1949). Of these compounds para-phenylene diamine is in general use as a hair dye and is known to cause dermatitis occasionally in susceptible subjects.

An interesting case of systemic poisoning resulting in death from subacute atrophy of the liver in a female hairdresser's assistant aged 21 was reported by Israëls and Susman (1934). In this case there appears to have been no skin disease attributable directly to the para-phenylene diamine. Rubber gloves were used to apply the dye and the gloves were removed for the shampoo which followed. The stained hands were treated with hydrogen peroxide and this was considered to be a possible contributory cause of death.

Occasionally workers have been seen who have had resin or amine splashes on the unprotected skin and have not reported any ill effects. There are also those who develop mild attacks of transient erythema and minimal eczematous lesions of the hands, who, when the skin has cleared, continue epoxy resin work without further involvement. This " hardening " effect has been reported in many chemical workers but in epoxy-amine processes appears to be much less common. Hellier (1958) has suggested that hardening may be due to an " immunological process or may simply be the result of mechanical toughening of the skin ".

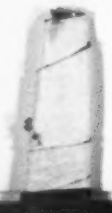


FIG. 18.—Bulla from patch test with ethylene amine.

Prophetic patch testing in the selection of staff appears to us to be of no value. A positive reaction may be expected in practically all those who are submitted to the amines in the strengths used in these processes. As long ago as 1949 one of us (L.B.B.) submitted a worker to a test with the smallest possible amount of an ethylene amine with the result shown in Fig. 18. The bulla formed rapidly, took several weeks to heal, and left a permanent scar.

Patch testing in those who have dermatitis from resins is in our opinion indefensible. Malten (1956), investigating the effects of epoxy resins, carried out an extensive series of patch tests in Holland. In all 157 substances used in plastics were tried in varying concentrations. The results were not convincing, but he did conclude that " workers making and using synthetic resins formed by polycondensation are exposed to greater occupational hazards than those working with synthetic resins formed by polymerization ". The results of all patch testing are notoriously variable and Von Haam and Mallette (1955), investigating the effects of plastics, found that " their previously published results with 90 irritating compounds are probably erroneous and are retesting all those showing positive reactions ".

Lauer (1956) has summarized the position of the industrial physician adequately as follows:

> " Preplacement patch tests with substances encountered in the occupation have been advocated but the author does not subscribe to routine preplacement patch testing, because if the worker has never come into contact with them, careful questioning should elicit his hypersensitiveness. Patch tests may give negative results but will not foretell whether the person will become sensitized with this substance."

Splashes in the eyes cause acute pain and conjunctivitis. Savitt (1955) applied ethylenediamine and diethylenetriamine to the eyes of rabbits and caused severe corneal damage. Similar effects occurred when the same substances were diluted to 15% in water, but a 5% dilution caused only minor injury. Employees occasionally complain of inability to focus and a halo effect around objects focused upon.

There were no signs of other central nervous system involvement, difficulties of respiration (other than those already noted), or of gastric upset, but the results of Hine *et al.* must be considered when cases of long-term exposure are eventually investigated.

As many specifications include the use of fillers which are added to the resin mixture, commonly chalk, mica flour, and silicates, care must be exercised in the mixing, as the continuous inhalation of silicates may cause lung disease and it would be a wise precaution to use only large mesh size powders.

Headache is commonly complained of but is usually transient.

We have not seen nor are we aware of reports of neoplastic skin changes from epoxy resins or amines, although it has been suggested, as a result of the work of Hendry, Homer, Rose, and Walpole (1951), that bis-epoxides may be carcinogenic, but it must be pointed out that they worked with considerably higher molecular weight chemicals than those in use in the resins we are considering. Whitby (1957), who has studied these resins for a considerable time, is of the opinion that the molecular weight of a resin is important in relation to its toxicity and that the commercially available resins are much less soluble in body fluids than those used by Hendry and his associates. He also considers that " when the resin is cured by higher polymerization and cross linkage the irritant effect goes down enormously ".

Incidence

There are now reports to show that in unprotected workers a very high incidence may be expected. In the U.S.A. it has been stated (Borden Co., 1955) that " epoxy resins and amine hardeners are the greatest single source of contact dermatitis in industry today ". An experienced industrial physician who visited several factories in the U.S.A. reported: " In 1954 I was in several factories in the States where motor car bodies were being made with epoxy resins and in these it was common for the occupiers to admit to a 75% incidence of dermatitis, but while walking round it was very difficult to see anyone who was not showing signs of dermatitis of the hands, arms or face, so I would put the incidence nearer to 100% " (Reynard, 1958).

Grandjean (1957) reported an incidence of 50% in 328 workers in factories in four countries. Reports of considerable involvement are available from most European countries. Malten (1956), in his survey in Holland, reports a high incidence after investi-

Savitt (1955) painted undiluted amine on the skin of the belly of rabbits and reported " severe corrosive reaction with toxic effect ". When he diluted the amine to 10% in water, the skin reaction was eliminated. This does not appear to be a satisfactory criterion as the amines are used undiluted in industry.

As previously pointed out, the reaction between an epoxy resin and curing agent is exothermic and may be considerable, as much as 60 calories per gram being generated, but in common with other observers we have not as yet noted any skin burns from this.

In general the amines may be classified as direct primary irritants and also may act as secondary sensitizers. Cross sensitization with other amines has been noted in laboratory workers where short-term exposures to many amines are usual and also in factories where a process has been changed. It is generally held that the epoxy resins are less liable to cause skin reactions, but Hine and his colleagues (Hine *et al.*, 1956) found that glycidol and the glycidyl ethers cause irritation of the skin ranging from erythema to eschar on cutaneous application, but all produced some irritation.

Attention has been drawn to the greasy pitted appearance of the air-free surface of moulded blocks of resin and its high *p*H. This film disappears when the surface is subjected to heat but returns when the resin recools and eventually may disappear altogether on repeated heating. This surface effect may well have been the cause of dermatitis in a patient with a prosthesis made of a resin-amine mixture.

A man with a partially amputated arm was fitted with a prosthesis made of epoxy resin-amine lamination. A few days after, a severe dermatitis developed in the stump, significantly in an area where some patching with resin had been carried out after the original casting. The prosthesis was then restoved for three days at 80°C. and was reapplied to the limb after the dermatitis had cleared. No further skin reaction was experienced. The exudate of high *p*H material may well have been the cause of dermatitis in this case.

The working of the finished resin product does cause serious problems, particularly where employees have become sensitized. The fine dust which arises when laminates or castings are machined, drilled, sandpapered, or filed causes marked irritation or erythema of the mucous membranes and skin in spite of the opinions expressed by the suppliers of the raw materials that the so-called polymerized epoxy resin is safe.

A research engineer contracted dermatitis in developing new combinations of epoxy-amines, became generally sensitized, and is now highly reactive to minute quantities in the atmosphere of any part of the resin mixture in any stage, cured or uncured, and if he enters a laboratory or shop where the finished product has been worked he flares up in under a minute. At one period he developed an acute psychosis as a result of the pruritus and had to be treated in a psychiatric hospital.

A manufacturer of sports equipment purchased rod sheet and fibre glass laminates of epoxy resin for use in making tennis racquet frames, golf club handles, etc. During the machining and working of this material, cases of dermatitis developed in practically all those at risk as a result of the powder given off by the material.

Phenylene diamines have been recommended, particularly metaphenylene diamine, which is used where special heat-resisting polymers are required. In this process the meta-phenylene diamine in powder is heated until it is molten and then mixed with the resin. The whole operation should be carried out in a fume cupboard, as the meta-phenylene diamine sublimes, contaminates the atmosphere, and settles on neighbouring objects and eventually causes brown staining of the skin but no irritation. It should be noted that the phenylene diamines, toluene diamines, and other alkylated benzene diamines and the salts of these compounds are included in the schedules of the Poisons List (1949) and the Poison Rules (1949). Of these compounds para-phenylene diamine is in general use as a hair dye and is known to cause dermatitis occasionally in susceptible subjects.

An interesting case of systemic poisoning resulting in death from subacute atrophy of the liver in a female hairdresser's assistant aged 21 was reported by Israëls and Susman (1934). In this case there appears to have been no skin disease attributable directly to the para-phenylene diamine. Rubber gloves were used to apply the dye and the gloves were removed for the shampoo which followed. The stained hands were treated with hydrogen peroxide and this was considered to be a possible contributory cause of death.

Occasionally workers have been seen who have had resin or amine splashes on the unprotected skin and have not reported any ill effects. There are also those who develop mild attacks of transient erythema and minimal eczematous lesions of the hands, who, when the skin has cleared, continue epoxy resin work without further involvement. This " hardening " effect has been reported in many chemical workers but in epoxy-amine processes appears to be much less common. Hellier (1958) has suggested that hardening may be due to an " immunological process or may simply be the result of mechanical toughening of the skin ".

FIG. 18.—Bulla from patch test with ethylene amine.

Prophetic patch testing in the selection of staff appears to us to be of no value. A positive reaction may be expected in practically all those who are submitted to the amines in the strengths used in these processes. As long ago as 1949 one of us (L.B.B.) submitted a worker to a test with the smallest possible amount of an ethylene amine with the result shown in Fig. 18. The bulla formed rapidly, took several weeks to heal, and left a permanent scar.

Patch testing in those who have dermatitis from resins is in our opinion indefensible. Malten (1956), investigating the effects of epoxy resins, carried out an extensive series of patch tests in Holland. In all 157 substances used in plastics were tried in varying concentrations. The results were not convincing, but he did conclude that " workers making and using synthetic resins formed by polycondensation are exposed to greater occupational hazards than those working with synthetic resins formed by polymerization ". The results of all patch testing are notoriously variable and Von Haam and Mallette (1955), investigating the effects of plastics, found that " their previously published results with 90 irritating compounds are probably erroneous and are retesting all those showing positive reactions ".

Lauer (1956) has summarized the position of the industrial physician adequately as follows:

> " Preplacement patch tests with substances encountered in the occupation have been advocated but the author does not subscribe to routine preplacement patch testing, because if the worker has never come into contact with them, careful questioning should elicit his hypersensitiveness. Patch tests may give negative results but will not foretell whether the person will become sensitized with this substance."

Splashes in the eyes cause acute pain and conjunctivitis. Savitt (1955) applied ethylenediamine and diethylenetriamine to the eyes of rabbits and caused severe corneal damage. Similar effects occurred when the same substances were diluted to 15% in water, but a 5% dilution caused only minor injury. Employees occasionally complain of inability to focus and a halo effect around objects focused upon.

There were no signs of other central nervous system involvement, difficulties of respiration (other than those already noted), or of gastric upset, but the results of Hine *et al.* must be considered when cases of long-term exposure are eventually investigated.

As many specifications include the use of fillers which are added to the resin mixture, commonly chalk, mica flour, and silicates, care must be exercised in the mixing, as the continuous inhalation of silicates may cause lung disease and it would be a wise precaution to use only large mesh size powders.

Headache is commonly complained of but is usually transient.

We have not seen nor are we aware of reports of neoplastic skin changes from epoxy resins or amines, although it has been suggested, as a result of the work of Hendry, Homer, Rose, and Walpole (1951), that bis-epoxides may be carcinogenic, but it must be pointed out that they worked with considerably higher molecular weight chemicals than those in use in the resins we are considering. Whitby (1957), who has studied these resins for a considerable time, is of the opinion that the molecular weight of a resin is important in relation to its toxicity and that the commercially available resins are much less soluble in body fluids than those used by Hendry and his associates. He also considers that " when the resin is cured by higher polymerization and cross linkage the irritant effect goes down enormously ".

Incidence

There are now reports to show that in unprotected workers a very high incidence may be expected. In the U.S.A. it has been stated (Borden Co., 1955) that " epoxy resins and amine hardeners are the greatest single source of contact dermatitis in industry today ". An experienced industrial physician who visited several factories in the U.S.A. reported: " In 1954 I was in several factories in the States where motor car bodies were being made with epoxy resins and in these it was common for the occupiers to admit to a 75% incidence of dermatitis, but while walking round it was very difficult to see anyone who was not showing signs of dermatitis of the hands, arms or face, so I would put the incidence nearer to 100% " (Reynard, 1958).

Grandjean (1957) reported an incidence of 50% in 328 workers in factories in four countries. Reports of considerable involvement are available from most European countries. Malten (1956), in his survey in Holland, reports a high incidence after investi-

gating all the known substances with which the workers came into contact. In Great Britain there have been many cases and compensation has already been awarded by the High Court for dermatitis from this cause. Actual figures are not available, but in the factories inspected by us the incidence of those at risk has varied from 100% down to 20%.

Discussion

There is no doubt that epoxy resins/amine curing systems can now be considered as toxic. Amines are more chemically reactive than epoxy resins and are capable of producing considerable pathological disturbance although the resins are less likely to do so. The resin/amine systems do not form completely polymerized inert products and in the course of curing produce volatile materials which may cause dermatitis, inflammation of the mucous membranes, skin allergies, less commonly respiratory distress, and occasionally other symptoms such as liver dysfunction or visual disturbance. Ingestion of the resin, which is unlikely in industry, has been tested in animals and appears to have caused little upset, but although there are no reports of ingestion of amines in man it is likely that severe poisoning would result. There are no reports of carcinogenic activity in the industrial field, but the suggestion has been made that such activity is possible. Blood disorders have not been noted. Delay in the development of symptoms varies from hours to weeks after exposure and cross sensitization to other compounds in epoxy/amine systems is frequent. The sensitization may last for long periods.

Examination of the cured resin confirms that there is a complex chemical mixture formed which may consist of reacted or unreacted amines, plasticizers where used, and many possible unidentified intermediate products as the result of the interaction of the components of the system.

Plasticizers appear to play some part, as resin systems which do not use them produce far fewer bubbles. The products of all the systems produce materials with relatively high *p*H levels and these values remain for long periods. The greasy air surface of cast blocks may be an exudate of unreacted amine or other organic material of high *p*H. Extraction of amine from the so-called polymerised resin gives a relatively high percentage of amine in unreacted state. Amines are well known as primary skin irritants and also as sensitizers (Schwartz, Tulipan, and Birmingham, 1957), and, as in all the specifications the amine values are relatively high, these will, in our opinion, account for most of the cases of contact dermatitis. The hot amine vapour emitted during curing operations attacks the conjunctivae and the more sensitive skin of the face, as would be expected.

Although varying the concentrations of amine in a resin/amine mixture does not appear to alter the appearance of the finished product, it was surprising to find that amine concentrations as low as 1:14 produced a film showing large amounts of unreacted material (Fig. 15) with a relatively high surface *p*H value which would be likely to be as great a risk as mixtures containing larger amounts of amine. The plasticizer may be in part responsible for this. As most of the dermatitis cases seen were caused by the use of this resin, there is no doubt that more care must be exercised in its use. The heat treatment of the resin/amine system markedly reduced the surface *p*H and within the body of the resulting product there were fewer bubbles. Atmospheric conditions appear to be of importance in cold cures as mixtures allowed to harden in high relative humidity gave the highest *p*H recorded (11+).

The cases of dermatitis and sensitization which have resulted from the working of hardened resin (by sawing, filing, etc.) are not surprising as the fine powder may contain 1% of amine in the unreacted state. The heat developed by the fast moving tool will tend to increase the liberation of unreacted volatile materials. The sensitization of the mucous membrane of the nasal mucosa and conjunctivae is acute and may be profoundly disturbing.

In view of the known risk from amines, the replacement of these by amides is desirable in those factories where trouble-free and no-touch techniques cannot be introduced. On the evidence of freedom from bubbles in the mixtures this would be justified.

The epoxy resins and glycidyl compounds are possible hazards, but appear to be less likely to cause trouble if handled with reasonable care. As it is possible to meet most of the demands of industry with resins not containing plasticizers there seems to be no object in their general use. Nevertheless, as indicated above, the substances of which epoxy resin is composed, *i.e.*, epichlorhydrin and diphenylolpropane, are both irritants (Hine *et al.*, 1956) and we have been informed (Narracott, 1953) that it is possible for chemical manufacturers to produce these and combine them by modern installations with little risk to the process workers.

A confirmation of our finding that air-cured resins are likely to be more harmful to the skin is given in a recent report by Gaul (1957) who in investigating dermatitis due to epoxy resin with phthalic anhydride hardener came to the following conclusions:

> " A fresh sample of air cured resin was as allergenic as the liquid resin. This appears to indicate that the use of air cured epoxy resins could lead to numerous

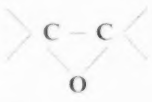
sources of sensitization. Liquid epoxy resin proved to be the allergen with the sensitizing component directed to the bisphenol A. The patch test reactions were almost perfect reproductions of the irritation from adhesive tape."

Gaul carried out patch tests with 1% concentrations in olive oil. This, we think, can lead to difficulties in interpretation. In any case, the concentrations bear no relationship to actual use and although he tested T.E.T., butyl phthalate, and phthalic anhydride with negative results, this may have been due to dispersion of the allergen or retardation of absorption through the use of olive oil. We have seen similar negative results when paraffin molle was used with amines and epoxy resin although it is certain in Gaul's case that the man tested had dermatitis while using these chemicals.

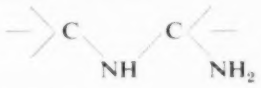
It seems that much of the trouble caused by the introduction of the epoxy resins and amine and amide hardeners into industry has resulted from the failure of responsible authorities to recognize that they are dealing with highly reactive chemicals. There is some awareness that when resin and hardeners are mixed, a reaction takes place, but this reaction is often thought to be specific to the system involved, and the average users of these resins do not seem to realize that chemical activity and biological activity are inseparable. Indeed biological activity in this sense is merely a synonym for chemical activity in a biological system.

The chemical groupings associated with these systems,

the epoxy group



and the polyamine group,



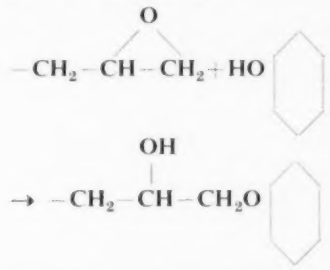
are both highly reactive even at room temperature, as is shown by the use of compounds containing these groups in the so-called cold-curing processes.

There is therefore no *a priori* reason why either of these types of material should not enter into reaction with biological systems under the same mild conditions.

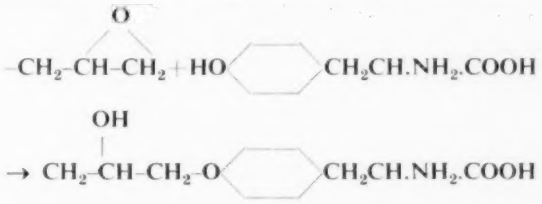
In the unpolymerized forms both the resins and the catalyst are materials of low molecular weight which are readily miscible with skin secretions and consequently can penetrate rapidly and easily into the sensitive lower layers of the skin; in addition, the volatility of the lower amines allows their entry into the body by ingestion and inhalation.

Once these reactive molecules have passed into the body in this way, it is reasonable to postulate a combination between them and the reactive groupings of a protein.

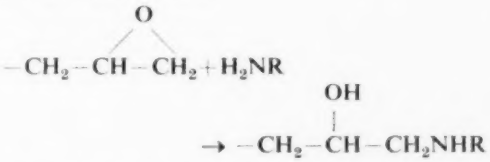
For example, the free epoxy end-group of a resin is known to react with phenols



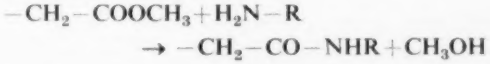
and a reaction can thus be imagined between the tyrosine residue of a protein and an epoxide resin.



A similar reaction might occur with amines and the reaction between an epoxy resin and the primary amine group of a catalyst is formally similar to that between the resin and the primary amine group associated with, say, the amine-acid lysine incorporated into a protein.



The amine catalysts themselves can also react with proteins where amino-acid residues carry terminal ester groups



Protein molecules modified in this way may possess the properties of antibodies and these may be responsible for the severe sensitization reactions often encountered in industrial exposure to the amines and hardeners.

This purely theoretical approach to the mechanism whereby these substances exert their physiological

effects has the following important practical consequences:

(*a*) No resin and hardener system capable of reacting at normal temperatures can be regarded as physiologically inert.

(*b*) It is impossible to produce such a system which is completely non-toxic since chemical and biological activity are inseparable.

(*c*) Minimum toxicity should be associated: (i) with minimum volatility of the components; (ii) with minimum solubility in skin secretions.

(*d*) It seems to be an experimental fact that the risk of sensitizing an individual to these materials is proportional to the integrated exposure (concentration $\times$ time) to which he is subjected. Once an individual is sensitized, the slightest contact with the offending material will provoke an immediate reaction.

It follows that the risk of sensitization can be minimized if (1) pollution of the atmosphere is avoided. (2) The material is prevented from coming into contact with the skin. (3) Where contamination of the skin is unavoidable, suitable barrier cream should be used to minimize the risks of penetration. (4) Deposits of resin should not be allowed to accumulate upon the skin but should be cleaned off as frequently as circumstances permit.

Point (1) implies good ventilation technique. Special attention should be paid to ensuring that fresh air passes first over the worker then over the work, and then to the extraction system.

Point (2) requires the introduction of no-touch technique whenever possible.

Point (3) is now well recognized in industry and the manufacturers of resin recommend the use of barrier creams in their technical literature. These creams should be of the water-repellent type as aliphatic amines are water soluble and sweat penetrating through a water-soluble cream will leach the amine back into the skin.

Point (4) is much less well understood. The uncured or partially cured resins are readily soluble in such solvents as methyl ethyl ketone or toluene. This fact has led to the widespread use of such solvents for cleansing the skin. It is not fully realized, however, that apart from waste and fire risk this habit is extremely reprehensible from the point of view of industrial hygiene. The solvent may remove some of the contaminant but spreads the rest over the skin besides facilitating its penetration. The use of soap and water to remove resins is often recommended but simply does not work if the resin has been in contact with the skin for any length of time. Soap and water is equally ineffective in removing traces of resin after washing in solvents.

A third and equally undesirable practice is to allow the resin to harden completely and then to pick it off the skin. This is an effective method of removing epidermis and renders the underlying skin even more vulnerable at the next contamination, particularly around the nails.

In an effort to solve this problem, a cleansing cream has been produced which combines solvent and detergent properties. Both the solvents and emulsifying agents used have been specially selected to give the minimum of dermatological offence.

The mechanism of action of the cream is as follows:

The solvent phase quickly dissolves the resin and the resulting solution is rapidly re-emulsified into the cream. Since the cream has an aqueous external phase, the solvent is not normally in contact with the skin either before or after picking up the contaminant. Furthermore, creams of this type are non-inflammable and any residues are compatible with soap and water.

The use of this cream is desirable even when the hazard of skin irritation is considered unimportant, since under production conditions, the impairment of manual dexterity due to an accumulation of resins on the skin is an important factor, as is the time wasted in inefficient methods of cleansing.

Handling Precautions

Experience has shown that it is now possible to avoid or reduce the hazards of these materials by efficient factory techniques. The ideal installation would be a complete no-touch system but this is usually not practicable. We have found that the following are essentials which can be applied to the smallest factories:

(1) Instruction and education of all staff.

(2) Only limited quantities of materials, particularly solvents, must be made available from stores. In practice this should be restricted to that amount necessary for the shift or at most for the day's work.

(3) A routine technique should be adopted so that one complete cycle of operation takes place, *i.e.*, weighing, mixing, de-aerating, pouring, stoving.

(4) Mixing and de-aerating should take place in well-ventilated chambers under cowling or in fume cupboards. Extraction fans must discharge to the outside air. Hot processes should be totally enclosed. If possible the process should be housed in a special unit. Where exhaust ventilation is not possible, fans of reasonable size should be installed to blow air away from the operator.

(5) No smoking or consumption of food at work.

(6) Benches should have easily cleaned surfaces or covers which can be changed when soiled.

(7) For the cold (or air) cure process, work

should be stored in well-ventilated chambers where restricted entry can be maintained.

(8) Paper cups which are frequently used to mix resins must be disposed of to avoid further contamination and are best destroyed by incineration outside the works.

(9) Full advantage must be taken of industrial hygiene: (*a*) Suitable barrier creams must be provided at the work bench and used regularly. (*b*) Resin-removing cream must be available at the work bench with a supply of clean rag or paper towels. (*c*) Protective clothing should be used and face masks if powders are used. Sleeveless overalls avoid impregnation of cuffs. (*d*) Good washing facilities on site.

(10) Pre-employment selection of workers to exclude those with a history of chronic skin disease, allergy, and asthma.

(11) All skin involvements and injuries should be reported immediately.

(12) Thorough cleansing of the hands before using lavatories.

References

Bakelite Ltd. (1957). Technical Memoranda, June. London.

Borden Co. (1955). Casco Service Bulletin No. 8a. New York.

Bourne, L. B. (1957). *Practitioner*, **179**, 67.

Browning, E. (1953). *Toxicity of Industrial Organic Solvents*, rev. ed. 1952, p. 370. H.M. Stationery Office, London.

Dernehl, C. U. (1951). *Industr. Med. Surg.*, **20**, 541.

Gaul, L. E. (1957). *J. invest. Derm.*, **29**, 311.

General Mills (1957). Report on Non-Toxicity of Versamid Polyamide Resins, Kankakee, Ill.

Grandjean, E. (1957). *Brit. J. industr. Med.*, **14**, 1.

Hellier, F. F. (1958). *Brit. med. J.*, **1**, 196.

Hendry, J. A., Homer, R. F., Rose, F. L., and Walpole, A. L. (1951). *Brit. J. Pharmacol.*, **6**, 235.

Hine, C. H., Kodama, J. K., Wellington, J. S., Dunlop, M. K., and Anderson, H. H. (1956). *A.M.A. Arch. industr. Hlth.*, **14**, 250.

Israëls, M. C. G., and Susman, W. (1934). *Lancet*, **1**, 508.

Jacobs, M. B. (1941). *The Analytical Chemistry of Industrial Poisons Hazards and Solvents*, p. 573. Interscience, New York.

Lauer, D. J. (1956). *Penn med. J.*, **59**, 25.

Malten, K. E. (1956). *Verh. Ned. Inst. Prev. Geneesk.*, 32.

Narracott, E. S. (1953). *Brit. Plastics*, **26**, 120.

Pentz, P. G. (1957). Personal Communication.

Pletscher, A. Schuppli, R., and Reipert, R. (1954). *Z. Unfallmed. Berufskr.*, **47**, 163.

Reynard, W. J. (1958). Personal Communication.

Savitt, L. E. (1955). *A.M.A. Arch. Derm. Syph.*, **71**, 212.

Schwartz, L. Tulipan, L., and Birmingham, D. J. (1957). *Occupational Diseases of the Skin*, 3rd ed. London.

Shell Chemicals Tech. Bulletin (1954). May.

Von Haam, E., and Mallette, F. S. (1955). *Amer. industr. Hyg. Ass. Quart.*, **16**, 324.

Whitby, L. H. (1957). Personal Communication.

Brit. J. industr. Med., 1959, **16**, 98.

MEDICAL EXAMINATIONS FOR PUBLIC SAFETY*

BY

P. A. B. RAFFLE

From the London Transport Executive

(RECEIVED FOR PUBLICATION SEPTEMBER 9, 1958)

Driving buses in London is an occupation in which the standards of fitness have been defined and in which the frequency of, and clinical reason for, exclusion from the occupation have been recorded.

The criteria of fitness to drive a passenger vehicle are physical capability to handle controls (including good eyesight) and absence of conditions liable to cause sudden collapse or excessive fatigue with consequent liability to accidents. Some factors which may be overlooked as causes of collapse are idiopathic epilepsy which may first appear in middle life, carcinoma of the bronchus which commonly metastasizes in the brain and may cause fits, and laryngeal vertigo (cough syncope) which is much commoner in chronic bronchitics than is often realized.

When medical standards to maintain public safety and the man's own health were applied to applicants to drive London's buses, 5·3% of the applicants were rejected on general medical grounds and a further 13·3% were rejected for sub-standard vision and colour vision. All the applicants had experience of driving heavy vehicles and were otherwise acceptable as drivers.

Continued surveillance during working life, especially after sickness absence, of those involved in public safety is essential. During 1956, 23% of the examinations of bus drivers, who had been off sick for 28 days or more or for certain specified conditions, resulted in temporary or permanent exclusion from driving. This compares with 1·5% of examinations for licence renewal and 5·7% at age 65 and above.

Cardiovascular disorders accounted for 26% of the causes of rejection during 1956, one-third of these being due to hypertension and one-half to coronary heart disease. No one who has had clinical coronary heart disease is allowed to drive London Transport buses because of the known increased chance of recurrence. Periodic examinations revealed a number of hypertensives but the majority of the "coronary cases" were revealed by sickness absence. Electrocardiography at periodic examinations does not, at the present, enable those who will have coronary heart disease to be recognized.

Experience shows that the standards adopted are practicable and effective so far as bus drivers are concerned, and that careful assessment of fitness after sickness is as important as routine medical examination in maintaining public safety.

In order to judge the value of medical examinations in maintaining the safety of the public (or of a group of people working together) it is necessary to have two sets of information. The first is, what medical standards are adopted in determining the fitness of a man to enter into, or to continue in, an occupation in which public safety is involved. The second is, what clinical conditions most frequently render a man unfit to be employed in such an occupation in the judgment of those responsible for this decision, and on what occasions are these conditions recognized.

There is one occupation, driving buses in London, in which the standards of fitness adopted have been defined and in which the frequency of and clinical reasons for exclusion from the occupation have been recorded. In this paper, therefore, the medical standards for bus driving in London are briefly restated and some preliminary information is presented on the clinical conditions most frequently recorded as the reason for exclusion from driving, as determined by the doctors working in London Transport.

*A paper delivered in the symposium "The Assessment of the Value of Routine Medical Examinations in Industry" in the Occupational Health Section of the British Medical Association Annual Meeting on July 16, 1958.

Medical Standards

The British Medical Association (1954) and the World Health Organization (1956) published memoranda on medical standards for transport drivers.

Norman (1954) cites three criteria for safety which must be satisfied before a man can be considered fit to drive a passenger vehicle:—

(1) The driver must be physically capable of handling the controls of the vehicle for prolonged periods; all except minor physical abnormalities must be absent. His eyesight must reach a safe standard.

(2) He must not be suffering from any condition which is liable to cause sudden loss of consciousness or to interfere with the safe handling of the vehicle.

(3) He must not be suffering from any condition which is liable to cause excessive fatigue at the end of the working day, with consequent liability to accidents.

Fyfe (1958) has written of the practical aspects of carrying out medical examinations for public safety. Norman (1954 and 1958) lists the following conditions which may cause sudden loss of consciousness while driving:—Falling asleep at the wheel, epilepsy (idiopathic and other types), laryngeal vertigo (syncope caused by coughing), aural vertigo, hypertension, hypotension, coronary thrombosis, cerebral anaemia, aortic valvular disease, auricular fibrillation, pulmonary embolism, cerebral accidents, hypoglycaemia, and drugs.

There are three points about this list which are worth making because they tend to be forgotten (Norman, 1958). Idiopathic epilepsy may show itself for the first time in middle life. An epileptiform fit may be the first manifestation of a carcinoma of the bronchus; these tumours commonly metastasize in the brain and anyone who has been treated for a bronchial neoplasm should not be responsible for public safety. Laryngeal vertigo, or syncope due to coughing, occurs much more frequently than is generally realized; many chronic bronchitics, when closely questioned, will admit to having noticed the early stages of faintness during their morning bouts of coughing.

Pre-employment Medical Examinations

These medical standards, which experience has shown to be effective, have been applied for many years to the occupation of bus driving in London. It would be interesting to know how many applicants for employment as drivers failed to reach these standards on grounds of public safety alone. It is not possible to obtain this information because any such figures must include some instances where the reason for rejection is for the benefit of the applicant's own health as well as (or rather than) for the safety of the public. With this reservation, Table 1 shows the results of clinical pre-employment examinations of 18,003 applicants for driving buses or trolleybuses in London Transport during the years 1950-57.

TABLE 1

APPLICANTS FOR BUS DRIVING REJECTED ON MEDICAL GROUNDS BY LONDON TRANSPORT MEDICAL SERVICE 1950-57

Eyes	
Visual acuity	1,680
Colour vision	641
Pathological defects	36
Chest	
Lungs	112
Heart	245
Abdomen	
Gastric	52
Renal	21
Herniae	48
Nervous system	
Psychological	34
Neurological	34
Skin	
Dermatitis (industrial)	6
Other skin lesions	16
Limb defects	
Upper limbs	31
Lower limbs	26
Varicose veins	27
Rheumatism (including fibrositis and rheumatoid arthritis)	9
General diseases (diabetes—glandular diseases, etc.)	86
Ears	
Hearing	100
Pathological	149
Physique	14
Rejected	3,367
Total examined	18,003

All the men examined had satisfied an experienced lay interviewer that they were suitable for employment as a driver, were 24 years of age or more, and had recent heavy goods or passenger vehicle driving experience. It will be seen that 3,367 (18·6%) were rejected, but that 2,321 (71%) of the rejections were due to sub-standard vision or colour vision. One thousand and forty-six (5·3%) of the applicants were considered unsuitable for driving passenger vehicles on general medical grounds, especially public safety. A further 405 (2·3%), not included in Table 1, were temporarily deferred for investigation or treatment. The applicants were a highly selected sample of the population. They were self-selected by inclination to be a driver and subsequently a bus driver in London, and self-selected in the knowledge that a medical examination to a public safety standard was involved; and selected by interview and by previous driving experience as being suitable as bus drivers, yet there were 245 (1·4%) men with cardiovascular disorders warranting rejection. The disorders were mainly valvular lesions and hypertension. That there were also 149 (0·8%) men, many of them driving heavy vehicles for a living, with

pathological conditions of the ears, mainly chronic otitis media with its possibilities of aural vertigo, suggests that patients or doctors consider suppurative middle ear conditions to be of little importance.

The results shown in Table 1 are an argument for reintroducing the medical examination, which before 1940, was required before a heavy goods vehicle driving licence could be issued.

Routine Medical Examinations

The pre-employment medical examination is only one method by which doctors can help to maintain and increase the safety of the public. Because increasing age brings increasing prevalence of pathological conditions which may affect public safety, the continued surveillance of public service drivers is essential. This is recognized by the Licensing Authority in London which requires medical certificates of fitness at the renewal of Public Service Vehicle driving licences nearest the 50th, 56th, and 62nd birthdays, and annually from the age of 65. In addition to these statutory examinations and routine eyesight examinations, the London bus driver is required to be medically examined on the following occasions: Before return to work after absence due to sickness lasting more than 28 days, or accident lasting more than three days; after any sickness causing him to fail to complete a work shift; when he has been certified by his own doctor as suffering from vertigo, heart disease, epilepsy, or tuberculosis; and at any time at the request of the management. In addition, drivers are examined at their own request or at the request of their own doctors.

Results of Routine Examinations.—Table 2 gives the outcome of the medical examination of London Transport bus and trolleybus drivers during one year and shows the striking difference in the result of the examinations depending on the reason for which they were undertaken. During 1956 there were 5,416 examinations among the 17,153 drivers of all ages employed. Five hundred and two (9·2%) of these examinations resulted in the driver being temporarily or permanently taken off driving, either because of public safety or for the benefit of his health.

TABLE 2

CASES FOUND UNFIT FOR DRIVING AT ROUTINE MEDICAL EXAMINATIONS OF DRIVERS IN 1956

Reason for Medical Examination	Total Examined	No. Unfit
Vision	2,144	9 (0·4%)
Return from sickness absence	1,224	289 (23·6%)
Following accident	410	15 (3·6%)
Re-examinations*	577	124 (21·4%)
P.S.V. licence renewal	448	7 (1·5%)
Aged 65 and over	454	25 (5·7%)
Miscellaneous†	71	33 (46·4%)
Promotion to non-driving grades	88	—
Totals	5,416	502 (9·2%)

*At request of London Transport doctors.
†Mainly at request of the employee, his doctor, or his employer.

Of the examinations on return from sickness, 23·6%, and 21·4% of the re-examinations of those drivers under routine surveillance for some clinical condition observed on a previous occasion resulted in exclusion from driving compared with only 1·5% of the licence renewal examinations and 5·7% of the examinations of the highly self-selected group who decided to go on driving after the age of 65. The miscellaneous group of examinations contains those cases seen at the request of the employee, his doctor, or his employer. The high rejection rate found in this group is because many of the patients, on good grounds, had requested, or had been advised by their own doctor, a change from driving. This table shows that routine examinations at fixed intervals may result in diagnosis of conditions which have not yet taken the patient to his doctor, but that careful assessment after sickness is very important in promoting public safety and the health of a group of workers.

In carrying out all these examinations, and especially at the periodic examinations, it is often very valuable to study the patient's sickness-absence experience which is usually entered in his record of service. There may be recorded short spells of sickness absence of significance which have not previously occasioned medical examination.

Analysis of the cases found unfit demonstrates, not unexpectedly, the importance of disease of the cardiovascular system as a cause of exclusion from driving. In Table 3 the rejected cases from Table 2 (excluding those rejected at routine eyesight examination and at re-examination) are classified into broad diagnostic groups.

Functional Nervous Disorders.—The only diagnostic group, apart from cardiovascular disorders, which contains more than 10% of the rejected cases, is that of functional nervous disorders. It is significant that this group contains an appreciable number under the miscellaneous category of reason for examination. Some of these were drivers who had lost confidence in driving and, wishing to change their job, had requested a medical examination.

Organic Nervous Disorders.—The comparatively high figure of 8·1% of rejections for organic nervous disorders results from the inclusion of cerebrovascular accidents in this group. In fact, in order to complete the picture of the importance of the cardiovascular system as a cause of unfitness, 12 of

TABLE 3

REASON FOR EXAMINATION AND CAUSES OF REJECTION OF CASES FOUND UNFIT IN 1956

Broad Diagnostic Group No. *	Resuming after Sickness and Accident	Routine at Age 65 and Over	Public Service Vehicle Licence Renewal	Miscellaneous	Total	% of Cases Unfit
1. Tuberculosis	4	—	—	—	4	1·1
3. Neoplasms	19	1	—	—	20	5·4
4. Functional nervous disorders	33	1	1	13	48	13·0
5. Organic nervous disorders	28	1	—	1	30	8·1
6. Diseases of the eye	12	—	1	—	13	3·5
7. Diseases of the ear	10	—	1	2	13	3·5
8. Diseases of the circulatory system	75	12	4	6	97	26·3
9. Colds and influenza	4	—	—	—	4	1·1
10. Bronchitis	26	1	—	3	30	8·1
11. Other respiratory diseases	4	—	—	—	4	1·1
12. Diseases of stomach and duodenum	16	—	—	4	20	5·4
13. Hernia of abdominal cavity	1	—	—	—	1	0·3
14. Other diseases of the digestive system	4	—	—	—	4	1·1
16. Diseases of the skin	2	—	—	—	2	0·5
17. Diseases of bones and organs of movement	26	—	—	2	28	7·6
18. Accidents on duty	6	—	—	—	6	1·6
19. Accidents off duty	9	—	—	—	9	2·5
20. Miscellaneous	25	9	—	2	36	9·8
Totals	304	25	7	33	369	100

*For the International Statistical Classification code numbers included in the broad diagnostic groups see "Health in Industry: A Contribution to the Study of Sickness Absence: Experience in London Transport", 1956, Butterworth, London.

There were no cases in broad diagnostic group, No. 2, infective and parasitic diseases.

TABLE 4

REASON FOR EXAMINATION AND DIAGNOSIS OF CASES FOUND UNFIT BECAUSE OF DISEASES OF CIRCULATORY SYSTEM IN 1956

	Resuming after Sickness	Routine at Age 65 and Over	Public Service Vehicle Licence Renewal	Miscellaneous	Total
Angina pectoris	10	—	1	—	11
Coronary thrombosis	36	—	—	3	39
Hypertension	16	10	3	2	31
Miscellaneous	13	2	—	1	16
Totals	75	12	4	6	97

the cases, or a further 3·3%, should be transferred from this group to the cardiovascular group. This transfer has not been made because it would involve a major departure from the International Statistical Classification of Diseases, Accidents, and Causes of Death.

Bronchitis.—Laryngeal vertigo does not account for more than an important few of the rejections attributed to bronchitis. Anoxia, as manifested by cyanosis, and dyspnoea and tachycardia on slight exercise, is a much more important reason for exclusion from driving because of the possibility of slow reaction time and confusion brought about by diminished oxygen supply to the brain.

Diabetes.—The miscellaneous broad diagnostic group contains only one previously undiagnosed diabetic out of 902 routine age or licence renewal examinations. This driver was allowed to continue driving under regular medical surveillance, because his diabetes was controlled by diet alone. Men needing insulin are not considered safe to continue driving a bus.

Diseases of the Circulatory System.—Cardiovascular disorders, which accounted for more than a quarter of all the rejections, comprised 97 cases which are analysed by diagnosis in Table 4.

This shows that routine age and licence renewal examinations are valuable in ascertaining those with hypertension of a degree which makes it unsafe for them to continue driving. Only one of the 50 cases rejected on account of coronary heart disease was diagnosed at a periodic examination. This one case must not, of course, be scorned because he might just have been the driver who had a sudden disabling coronary thrombosis while driving.

Hypertension.—In this series, of the 31 cases found unfit for driving on account of hypertension, 13 (42%) were discovered at periodic examination but the majority were confirmed at examination following sickness absence (the two miscellaneous cases were referred to London Transport doctors by general practitioners).

When hypertension or its complications have caused sickness absence it is only occasionally that

the patient can be considered fit to drive again, even though hypotensive drugs have eliminated symptoms and reduced the blood pressure. These drugs depress cerebral activity and any patient taking them should be excluded from driving as an occupation. Hypertension discovered at routine medical examination often presents a difficult clinical problem and each case needs careful assessment. The men rejected in this series had either a blood pressure persistently above 200/100 mm. Hg at rest or some of the following: Symptoms (headache, dyspnoea, palpitations, claudication), cyanosis, tachycardia at rest, clinical or radiological cardiac enlargement, valvular lesion (especially aortic), pulmonary congestion, thickened peripheral vessels, diminished dorsalis pedis pulsation, hepatic enlargement, oedema, obesity, or albuminuria. Some of those rejected had blood pressures below 200/100 mm. Hg, but such symptoms and signs that they were considered unsafe for driving.

Coronary Heart Disease.—Coronary heart disease accounted for 13% of all the rejections for driving (Tables 3 and 4), and this excludes those 20 drivers who are known to have died, without resuming work, from this condition during 1956. (There were another 50 deaths from other causes.) Two questions often asked about coronary heart disease in relation to public safety are, Should a man who had had an overt "coronary thrombosis" continue in work involving public safety, and is it possible to predict at periodic examinations which of a group of men will develop coronary heart disease? A man who has had a "coronary thrombosis" is more likely to have another attack (as evidenced by sickness absence for this cause) than a man who has never had coronary thrombosis is to have his first attack. Morris, Heady, and Barley (1952 and 1957) and Morris (1958) showed, in their study of doctors, that those who have recovered from their first coronary episode may be as much as 10 times more likely to have a further attack than doctors who have never had coronary heart disease are to develop their first attack. There is some evidence that bus drivers are more likely to die in a subsequent attack than bus conductors. Morris and Raffle (1954) showed that the drivers' mortality from this condition up to three days and three months from the onset was twice that of the conductors. When those who survived three months were traced for three years, proportionately more former drivers than former conductors were found to have died from a subsequent attack. London Transport accepts the view that, in the interests of safety of the travelling public, a driver who has had clinical coronary heart disease should no longer drive.

The answer to the second question, Whether it is possible to pick out the future sufferer, is that in the absence of disclosed anginal symptoms, cardiac arrhythmias, or obvious peripheral or retinal arterial changes, there is no certain method of recognizing the patient who will develop clinical coronary heart disease. Heady, Morris, Lloyd, and Raffle (1954) showed that there was no significant difference in the previous sickness-absence experience of coronary and control groups. Electrocardiography is a useful confirmatory investigation when the clinical findings are suggestive. Routine electrocardiography at periodic examinations detects a few individuals who have had "silent coronaries", but the significance of minor changes in the electrocardiogram after exercise, in otherwise normal men, is unknown. Acheson (1957), for instance, found changes after exercise, usually considered indicative of coronary heart disease, in 5·3% of fit, symptomless R.A.F. personnel aged 19 to 39, and in 15·4% in those aged 40 to 54. What cannot be known without following these men up for many years is whether this type of change indicates a predisposition to future overt "coronary thrombosis". There is a great deal of research being done on this aspect of medical examinations for public safety. It is only when the results are available that it will be possible to assess the value of electrocardiography at periodic examinations in preventing collapses which might be dangerous to the public.

Master, Dock, and Jaffe (1939) among other authors, showed that the time of onset of coronary thrombosis was evenly spread over the 24 hours of the day. It is of interest that the occasion of onset of suddenly disabling coronary heart disease in 89 drivers in five years, all dying on the day of onset, also shows a random distribution (Table 5).

TABLE 5

OCCASION OF ONSET OF SUDDENLY DISABLING CORONARY HEART DISEASE IN 1953-57*

Onset while			
At wheel	11	at work 28	Total 89
Otherwise on duty	8		
Going to or from duty	9		
At home	40	not at work 61	
Known to be in bed	11		
On holiday or rest day	10		
(Men aged 35 to 64).			

*All died during day of onset.

One-third of the cases occurred in the (roughly) third of a driver's life spent at the wheel, otherwise on duty or near his garage going to or from duty. No reliance can, therefore, be placed on the probability of fatal collapses occurring off duty.

In only five of the 11 episodes occurring at the wheel did the driver not have sufficient warning of

the attack to stop the vehicle, in only three instances did the bus collide with another object and nobody was injured in these incidents (Norman, 1958).

Conclusion

In considering those conditions which render a man unfit for a job involving public safety, cardiovascular conditions have been stressed because experience shows that these are the conditions which cause more unfitness than any other for one occupation involving public safety—bus driving in London. When it comes to assessing the value of routine medical examinations for public safety, much reliance must be placed upon the experience of those organizations which are frequently involved in this work. Probably the only certain method of assessment would be to accept into employment all those rejected on present standards and to compare their safety and sickness records with matched control groups doing the same work. Not the most enthusiastic searcher after truth would dare suggest this! Reliance must therefore be placed on what experience has shown to be practicable and effective in many organizations which have a reputation for maintaining public safety, that is, important as the routine periodic examination is in maintaining public safety, equally important and probably more important, is the careful assessment of the patient's fitness to resume his occupation after a spell of sickness.

I am grateful to friends and colleagues, especially Dr. L. G. Norman, Dr. J. N. Morris, and Mr. F. H. Spratling, for much constructive criticism and encouragement in the preparation of this paper.

References

Acheson, E. D. (1957). *Lancet*, **1**, 26.
British Medical Association (1954). Memorandum on *Medical Standards for Road, Rail, and Air Transport*. London.
Fyfe, J. L. (1958). *Brit. J. clin. Pract.*, **12**, 512.
Heady, J. A., Morris, J. N., Lloyd, F. J., and Raffle, P. A. B. (1954). *Brit. J. industr. Med.*, **11**, 20.
Master, A. M., Dock, S., and Jaffe, H. L. (1939). *Amer. Heart J.*, **18**, 434.
Morris, J. N. (1958). Personal communication.
——, and Raffle, P. A. B. (1954). *Brit. J. industr. Med.*, **11**, 260.
——, Heady, J. A., and Barley, R. G. (1952). *Brit. med. J.*, **1**, 503.
——, ——, —— (1957). *Brit. Heart J.*, **2**, 227.
Norman, L. G. (1954). *Trans. Ass. industr. med. Offrs*, **4**, 3.
—— (1958). *Lancet*, **2**, 807.
World Health Organization (1956). *Guiding Principles in the Medical Examinations for Motor Vehicle Driving Permits*. Geneva.

THE JANUARY (1959) ISSUE

The January (1959) issue contains the following papers:—

Industrial Health—Meeting the Challenge. A. Meiklejohn.

The Toxicity of Epichlorhydrin Vapour. J. C. Gage.

The Response to Heinz Bodies in the Rat. Philip Rofe.

Toxic Solvents: A Review. Ethel Browning.

Investigations Concerning the Pre-radiological Stage of Silicosis. C. Velican, G. Latis, M. Popa, Gr. Popa, and M. Steinbach.

The Dust Content of the Lungs of Coal Workers from Cumberland. J. S. Faulds, E. J. King, and G. Nagelschmidt.

Respiratory Function and Disease among Workers in Alkaline Dusts. C. P. Chivers.

Quarry Bank Mill: Part 2. The Medical Service. Robert Murray.

Miscellanea:

Outbreak of Fever in Cotton Mills at Radcliffe, 1784. A Meiklejohn.

Occupation and Mortality:

Filial Mortality. J. A. Heady.

Mortality in Mining and Quarrying Occupations. D. D. Reid.

Mortality in Transport Occupations. C. J. Cornwall.

Book Reviews

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

Brit. J. industr. Med., 1959, **16**, 104.

MEASURING DUST EXPOSURE WITH THE THERMAL PRECIPITATOR IN COLLIERIES AND FOUNDRIES

BY

S. A. ROACH*

From the Pneumoconiosis Research Unit, Llandough Hospital, Nr. Cardiff

(RECEIVED FOR PUBLICATION OCTOBER 6, 1958)

The standard thermal precipitator has been modified for field surveys of airborne dust exposure so as to make it more portable. A microprojector is used when assessing the samples and for coal-mine dusts the counts are restricted to the range 0·5 to 5 microns.

In industrial environments the dust concentration appears to vary with a standard deviation of more than 50% of the mean. Part of this variability is due to errors of the thermal precipitator. The standard error of a count of a sample is about 10% to 15% in practical work and the combined effect of this and other errors is that the standard error of a single result is about 15%. However, in practice this can be neglected since the dust concentration itself is so variable. A more important source of error is the bias, due to overlapping among the particles on the cover glasses. The count may give a serious underestimate of the number of airborne particles if high sample densities are used.

The product of average concentration and duration of exposure is probably a good index of the dose of dust retained in a man's lungs. The duration of exposure is measured by a simple time study made at the same time as the concentration is measured.

Samples are taken near workers chosen at random to give unbiased estimates of the dust exposure. Ideally successive samples are taken alongside different workers. However, in a survey at a colliery it was not possible to do this and each day had to be spent with one collier. The mean dust exposure of the coal-getters was 2,860 particle-hours per shift, of those on stone work 2,250 particle-hours per shift, and the remainder had a mean dust exposure of 1,010 particle-hours per shift.

In a survey at a steel works successive samples could be taken alongside different workers. It was found that the dustiness was unrelated to the apparently dusty processes and as the dust was very fine it was suspected that it was the normal atmospheric pollution of the neighbourhood. This was confirmed by samples taken outside.

The cost of such surveys is found to lie between £1 and £2 per sample taken and consequently alternative instruments are being developed which can run unattended for long periods. In future research studies respiratory ventilation as well as dust exposure may be measured over many years, which, combined with periodic medical examinations, would enable the relation between dust exposure and its effects on the men to be determined.

In surveys of airborne dust conducted by the Pneumoconiosis Research Unit we aim to measure the amount of dust inhaled at work. Up to the present time most of the dust sampling has been done with the thermal precipitator (Green and Watson, 1935; Watson, 1936). This paper describes in detail the use of this instrument and the factors affecting its accuracy. Two surveys, one in a colliery and another in a steel foundry, are used to illustrate the differences in the techniques adopted and the results obtained.

*Present address: Occupational Health Unit, London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C.1.

Sampling with the Thermal Precipitator

The Apparatus.—The standard apparatus is fairly portable (Fig. 1a) but when set on its tripod it is easily knocked over and it cannot readily be operated while moving about. This is a serious disadvantage when

FIG. 1a.—Standard equipment.

FIG. 1b.—Portable equipment.

Photographs by National Coal Board, South Western Division Photographic Unit.

measuring the dust exposure of colliers since they may spend as much as two hours walking along a dusty underground roadway to and from their work and many of those employed on haulage work move about all the time. The modified apparatus illustrated in Fig. 1b uses a cap lamp battery with an ammeter, switch, and rheostat incorporated in the top cover plate. It is more portable than the standard instrument and easier to use in confined spaces. The thermal precipitator head is usually hung from a roof support when sampling in collieries but it can be fastened to a person's jacket or held in the hand for sampling close to the worker's face. A small reversible aspirator (Wright, 1954) replaces the can of water, jet, and measuring cylinder, used in the standard apparatus. The total weight of the modified equipment is 10 lb. compared with 24 lb. for the standard equipment.

Counting and Sizing the Dust.—A high power microscope with a travelling stage and a microprojector is used for counting and sizing the dust (Fig. 2). In the microprojector there are two front-silvered mirrors, which reflect the light on to a matt white card on the table in front of the observer where the image of the particles is easily seen. This makes viewing comfortable and free from eyestrain. Using a 2 mm. objective and × 10 eyepiece the magnification is about 2,500 times. A chain drive and flexible coupling control the fine focus and horizontal traverse. Back-lash is reduced by using spring mounts for the chain wheel bearings. A foot switch operates a counter leaving the hands free to

FIG. 2.—Microprojector for counting dust samples.

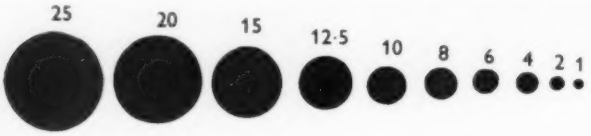
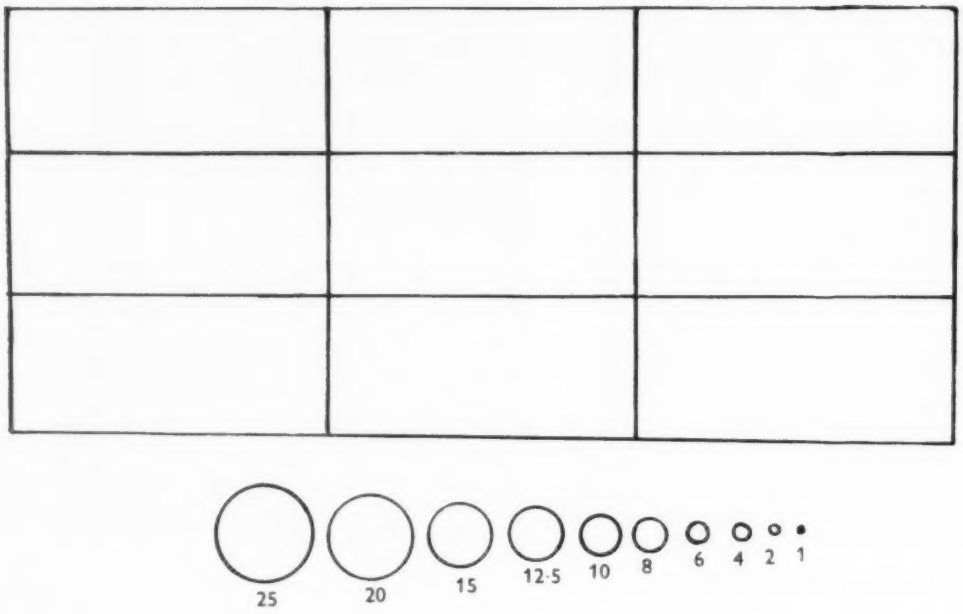


FIG. 3a.—A Patterson-Cawood graticule for detailed size analysis.



operate the controls. To reduce extraneous light the lamp and light beam are hooded and a curtain is hung between the operator and the microscope. The lamp base has screw controls for centering the light.

The size of the particles is estimated by comparing their area visually with those of a series of circles either on an eyepiece graticule or on the screen of the microprojector. Two graticules are illustrated in Fig. 3. The number of circles used depends upon the detail with which the size distribution is required (Patterson and Cawood, 1936; Fairs, 1943; May, 1945; Watson, 1952; Hamilton, Holdsworth, and Walton, 1954). The deposits are traversed beneath the microscope and the particles which pass through the graticule rectangle are counted.

The Size of Important Particles.—When determining the number and size distribution of samples

FIG. 3b.—A simplified graticule for routine counting.

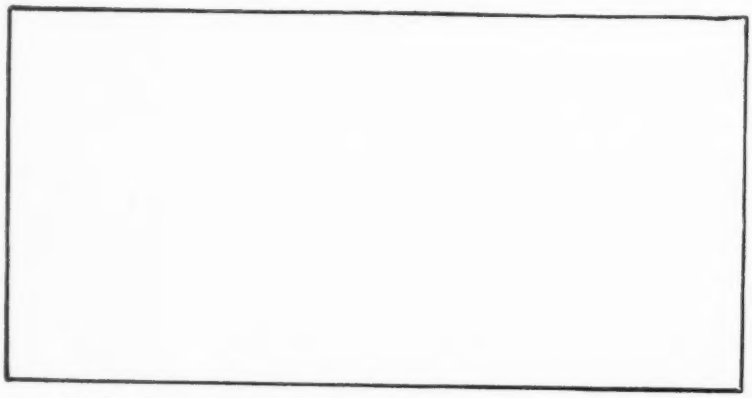


FIG. 3.—Graticules used in assessing the size of dust particles with a microscope.

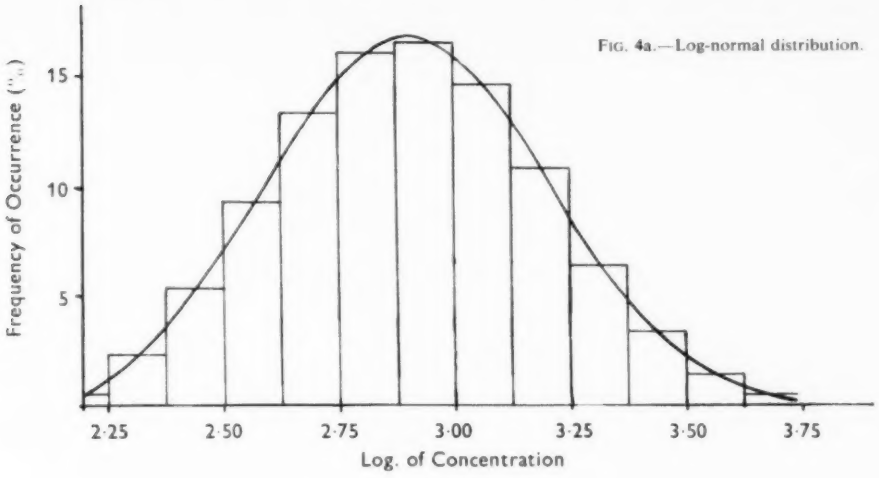


FIG. 4a.—Log-normal distribution.

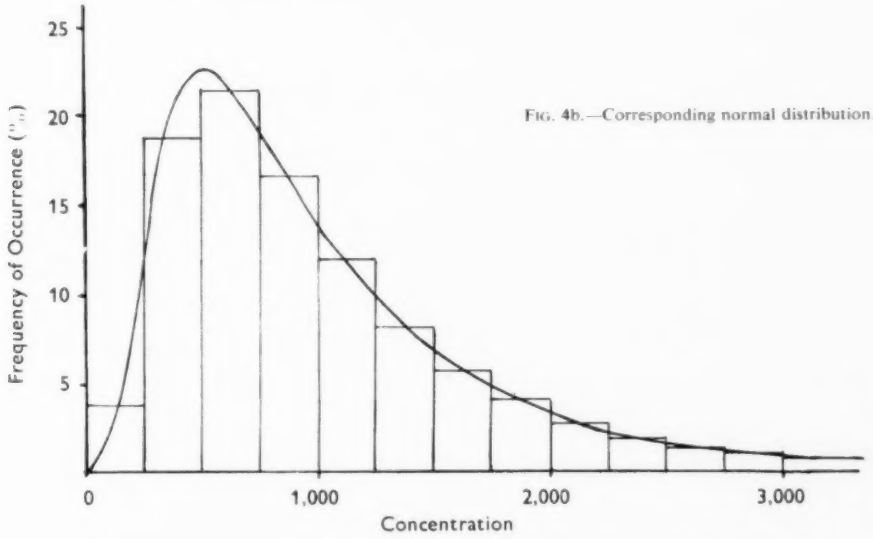


FIG. 4b.—Corresponding normal distribution.

FIG. 4.—The frequency distribution of concentrations.

in detail, eight samples can be assessed each day. More samples can be assessed if the sizing is simplified, and by using the graticule illustrated in Fig. 3b, 20 samples can be assessed each day. In addition, with simpler size analyses the results can be summarized and assimilated much more quickly. Consequently it is desirable to limit the sizing to no more than is essential for assessing the amount of dust of sizes likely to be retained by the lung.

When dust is inhaled the large particles are deposited in the upper respiratory tract and bronchi; only the small particles are carried into the alveoli where some of them are deposited. The probability of a particle reaching an alveolus and being deposited there depends mainly on its size and weight. The proportions of inhaled dust of different sizes deposited in the alveoli have been estimated theoretically by Findeisen (1935) and by Landahl (1950). Their results agree in general with the conclusions from indirect experiments on human subjects (see, for example, Brown, 1931 a and b; Van Wijk and Patterson, 1940; Landahl and Herrmann, 1948; Wilson and LaMer, 1948; Wilson, Sylvester, Laskin, LaBelle, and Stokinger, 1948; Davies, 1949; Brown, Cook, Ney, and Hatch, 1950; Landahl, Tracewell, and Lassen, 1951, 1952). They also agree in general with the results obtained by examining the size of the dust found in lungs after death (Gessner, Rüttner, and Bühler, 1949; Bedford and Warner, 1950; Cartwright and Nagelschmidt, 1951).

These studies show that very little dust is deposited in the alveoli of sizes greater than 5 microns in diameter and in coal-miners' lungs the greatest volume of dust lies in particles with diameters less than 5 microns and larger than 0·5 microns.

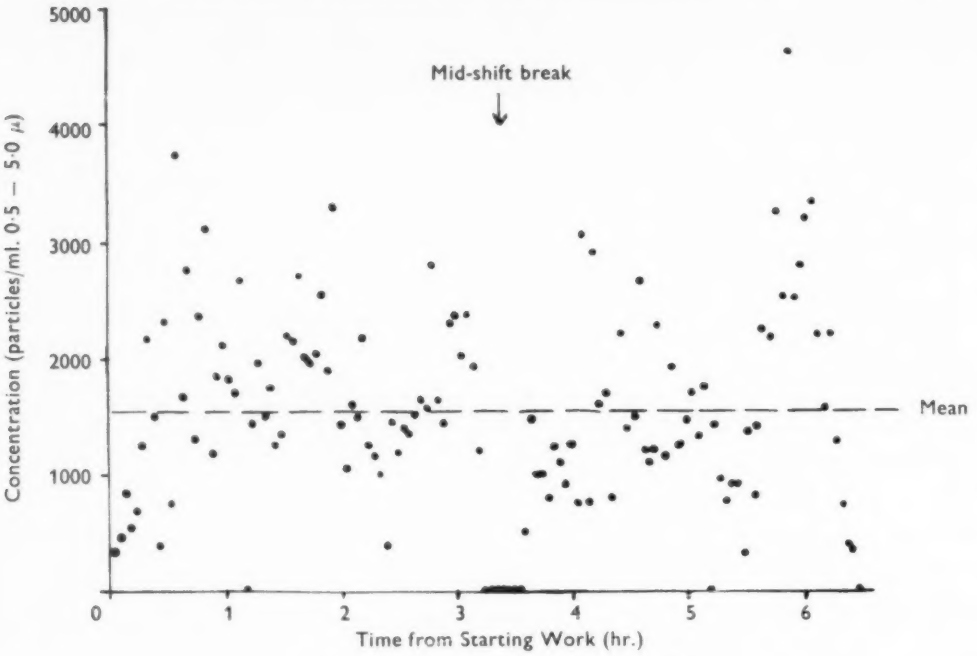


FIG. 5.—Variability of concentration during a day.

Thus in collieries the restricted count, 0·5 to 5 microns, is used, and this probably gives a good index of the volume of the dust likely to be retained by the lung. The count is obtained by using two circles on the graticule, one 0·5 and the other 5 microns diameter, and counting only those particles whose area lies between the area of these two circles. The result is then expressed as the number of particles per ml. of sizes 0·5 to 5 microns diameter. In other industries, where little is known about the nature and size of the dust, a full count and size distribution will help to assess the probable hazard and often to identify the source of pollution.

Variability of Counts

The Amount of Variability.—When a series of thermal precipitator samples is taken in an industrial environment the results are found to vary considerably.

The frequency distribution of counts gives the lop-sided, hump-shaped curve shown in Fig. 4a. However, if we take the logarithms of the concentrations we find the curve is usually roughly symmetrical and similar in shape to a normal distribution curve (Fig. 4b). Thus, by using the logarithms of the concentrations the extent of the variations in dustiness can be described in terms of the normal distribution.

The curves in Fig. 4 are for a lognormal distribution with a standard deviation of 0·3 log particles per ml. and an arithmetic mean concentration of 1,000 particles per ml.

Some of the variability in the results is due to the difference between the dustiness of different jobs but there is also a large variability in the dustiness from time to time in one place even when the work appears to be done at a steady rate. Fig. 5 shows the results of sampling alternately with two thermal precipitators at a coal-face during a coal-getting shift. Each sample was taken for a period of three minutes. A set of low concentrations occurred during the mid-shift break but apart from this the dust concentration fluctuated in a more or less random fashion from one sample to the next around the mean level of 1,550 particles per ml. Oldham (1953) analysed many sets of samples of this kind from different collieries and showed that within any given shift the logarithms of the concentrations at any one place are distributed about the mean with a standard deviation of 0·22 log particles per ml. When all places and shifts are included a standard deviation of 0·44 log particles per ml. has been found. This variation corresponds to standard deviations of the order of 50% and more of the mean.

Some of the variability arises in errors inherent in the thermal precipitator and in the way the samples are assessed. These errors are of various kinds, some of which can be studied separately.

Random Errors

Errors in Counting.—The size of the errors which

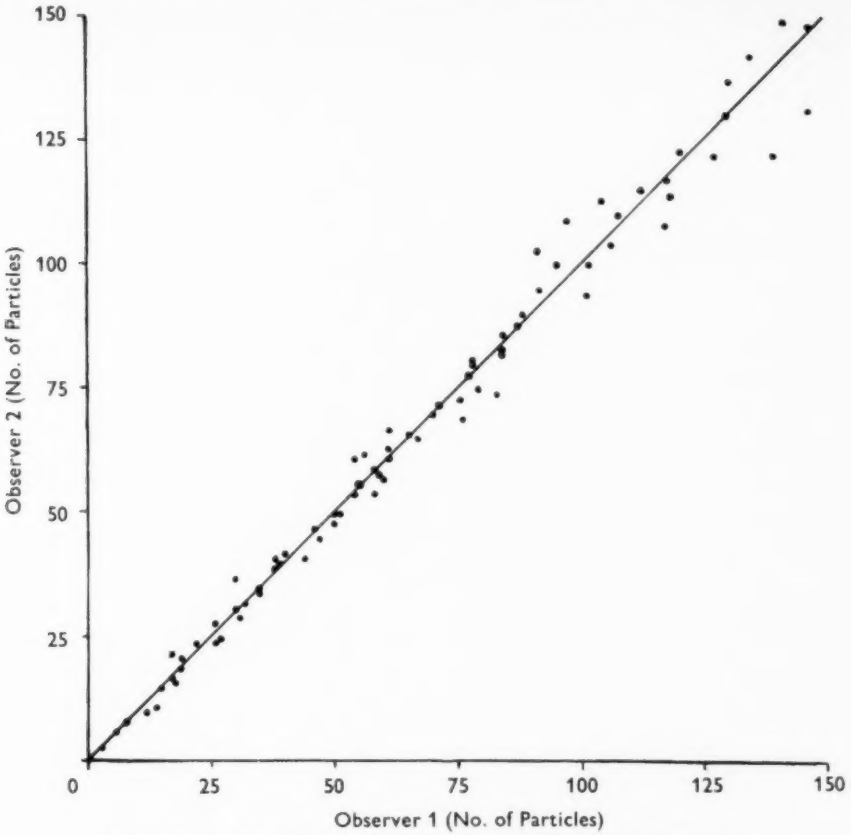


FIG. 6.—Counts of thermal precipitator samples by two observers counting together.

occur when counting a number of particles is illustrated in Fig. 6. This shows the results of a series of experiments in which two observers simultaneously counted the particles in a traverse across a sample using a microprojector. At the end of each traverse both observers wrote down the number of particles they had counted. The average difference between the two observers was 3·3 particles, about 5% of the count. Although this difference is small, it is perhaps surprising that the two observers counted the same number in only 11 out of 80 traverses. The main reason is that there is often a difference of opinion between observers on whether particles are larger or smaller than the graticule circles (Heywood, 1946; Watson and Mulford, 1954). Usually at least two traverses are counted on a sample, one on each of the two coverglasses on which the sample is distributed, which means that errors in counting of this kind are unlikely to give a standard error of more than 2% in the total count.

Number of Particles Counted.—Only a small fraction of all the deposited particles are counted (0·2% to 2·0%), a proportion determined by the width of the graticule within which the particles are counted in a traverse across the deposits and the number of traverses counted.

An important source of error is the variability of the number of particles in different traverses across the deposits. This is illustrated by the example in Fig. 7 which is a summary of the results of counting the particles in 184 traverses, each at a different point along the length of one deposit. The frequency histogram shows how the number of particles counted varied from 20 to 80. The mean count was 47 particles per traverse.

During the sampling, as the dust is precipitated, successive particles are equally likely to arrive and be deposited anywhere along the length of the sample. Under these circumstances, it can be shown that by chance alone we would expect to find that the number of particles in different traverses varies in a Poisson distribution. If the counting were perfect this means that the counts on different traverses would vary around the mean with a standard deviation equal

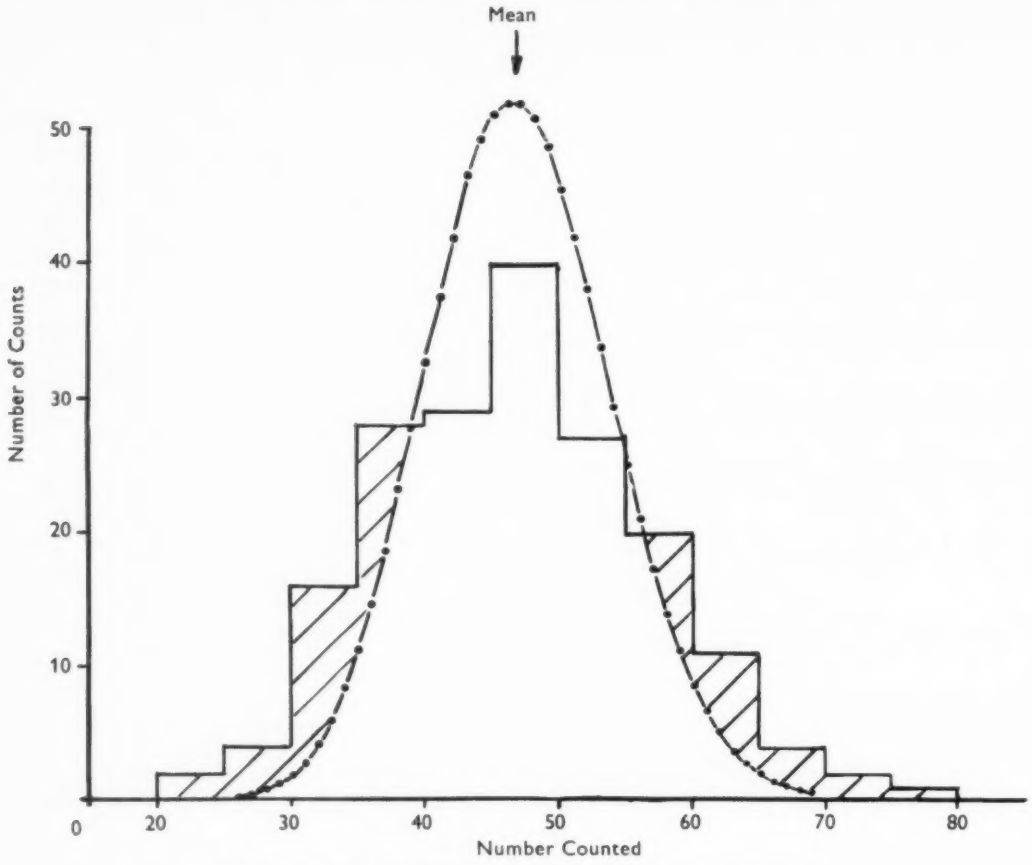


FIG. 7.—Size frequency histogram of counts of a thermal precipitator sample.

to the square root of the mean. Since the number counted on a traverse usually lies within the range 15-150 particles this irreducible variation would result in a standard deviation of 10% to 25% of the mean. In practice there is a further variation due to errors in counting. The dotted curve in Fig. 7 is the frequency distribution of counts expected from the Poisson distribution when the mean is 47. The additional variation shown by the actual counts is due in part to errors in counting and in part to the uneven deposition of the dust caused by the wire in the precipitator head not being perfectly straight and parallel to the two coverglasses.

If there were no counting errors the coefficient of variation would theoretically be larger for deposits with a low density than for deposits with a high density. The smooth curve in Fig. 8 shows the theoretical relation. Sometimes the particles are counted in two traverses at different points on the deposit and from the difference between such pairs of results an estimate can be made of the coefficient of variation of counts of a sample. The results of 1,000 pairs of counts from deposits of widely different densities were analysed to estimate this coefficient of variation. The results are illustrated in Fig. 8. It can be seen that in practice although the coefficient of variation did fall as the number counted increased, over the usual working range of 20 to 150 particles per traverse the coefficient was fairly constant at about 20%. If, as is usual in our work, an estimate of the number of particles on the sample is based on the mean of two such counts, one from each of the two deposits, then the standard error of such an estimate would be about 10% to 15% of the mean, this error being due to a combination of errors in counting and variations in the number of particles per traverse.

Beadle and Kerrich (1955) analysed the results of a comparison of counts by different observers counting the same samples. They showed that the bias between their observers was very small and the coefficient of variation fell from 17% for counts of

50 particles to 8% for counts of 250 particles and then remained roughly constant at 8% up to counts of 750 particles. These results are similar to those found by us where we have used similar densities.

A technician sometimes regards the difference between his successive counts of the same deposit as being due to his lack of care in avoiding mistakes and may in consequence produce results which agree to an extent which is unlikely to have occurred by chance. This may be done quite unconsciously and therefore as a routine no more than one traverse is counted across each deposit at any one time. When comparing repeat counts by the same observer Beadle and Kerrich (1955) found the coefficient of variation was less than the minimum variation predicted from the Poisson distribution. They were unable to account for this effect. Our experience suggests that this may have been due to the fact that the repeat counts were done with knowledge of the first counts.

Volume of Air Sampled.—The measurement of the volume of air drawn into the thermal precipitator for each sample may be in error. This affects the results since the concentration of airborne dust is given by the ratio of the estimated total number of particles deposited, derived from the traverse counts, to this volume of air. With the standard apparatus the volume of air aspirated through the thermal precipitator head is commonly measured with a 50 ml. measuring cylinder. When training technicians it is found that they sometimes misread the volume by 1 ml. or 5 ml. but it is difficult to judge to what extent such mistakes are likely to occur in practice with an experienced observer. Beadle and Kerrich (1955) measured the extent to which these mistakes may occur in the laboratory. They made 972 observations and in 49 of these (5%) a mistake was made of between 10 and 110 ml. in volumes varying between 75 and 570 ml. An error of 10— ml. was most common.

With the Wright reversible aspirator, used in the modified apparatus, the volume aspirated at each cycle is fixed at about 20 ml., and is measured once at the start of the shift and again at the end. This has the advantage that the volume is measured in the laboratory, away from the distractions of underground conditions, so that there is less likelihood of mistakes. The main source of error with this aspirator is from loss of water through the air outlet nozzle when reversing the bottles, especially if insufficient time is allowed for the aspirator to empty completely. After continuous use throughout a shift it is sometimes found that up to 2 ml. has been lost. In such cases the mean of the readings before and after the shift is used.

With both forms of aspirator the volume of air aspirated will be incorrect if there is a leak between the aspirator and the thermal precipitator head. This point can be checked in the laboratory with the aid of a bubble flowmeter.

Overall Repeatability.—The combined effect of all these errors on the repeatability of the results can be measured by taking samples simultaneously with two thermal precipitators side by side.

In experiments designed to measure the magnitude of the errors which occur in practice there are two important difficulties to overcome. First, it is necessary to exclude all possibility of spurious agreement. The memory of a previous result should be of no help to the observer in determining a particular value. The second difficulty is that in any experiment designed specifically to estimate errors the observers tend to be particularly careful. This cannot be avoided entirely but the longer the trial

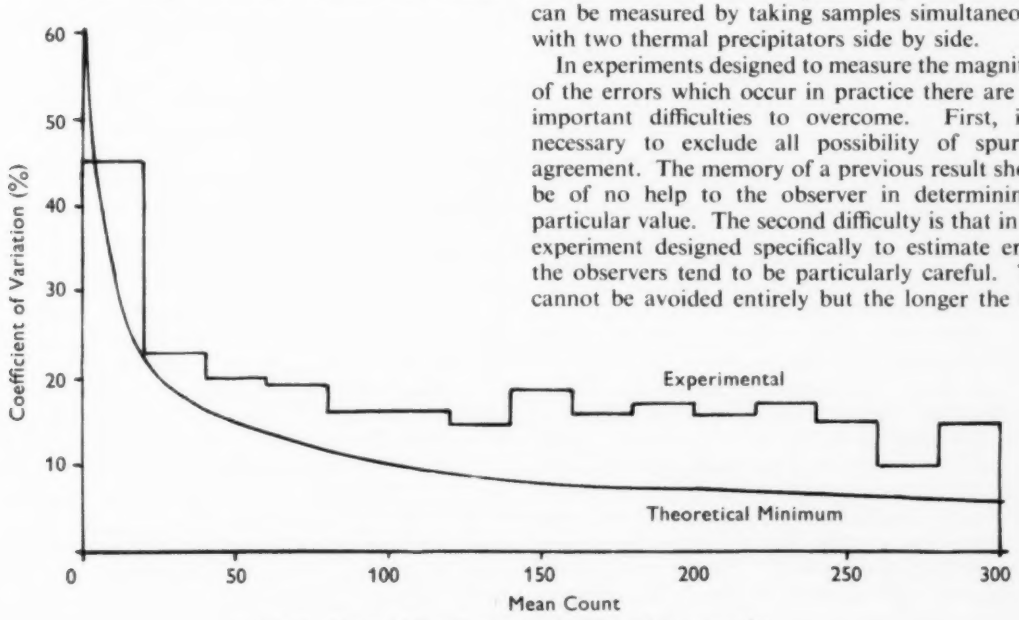


FIG. 8.—The variability of counts on thermal precipitator samples.

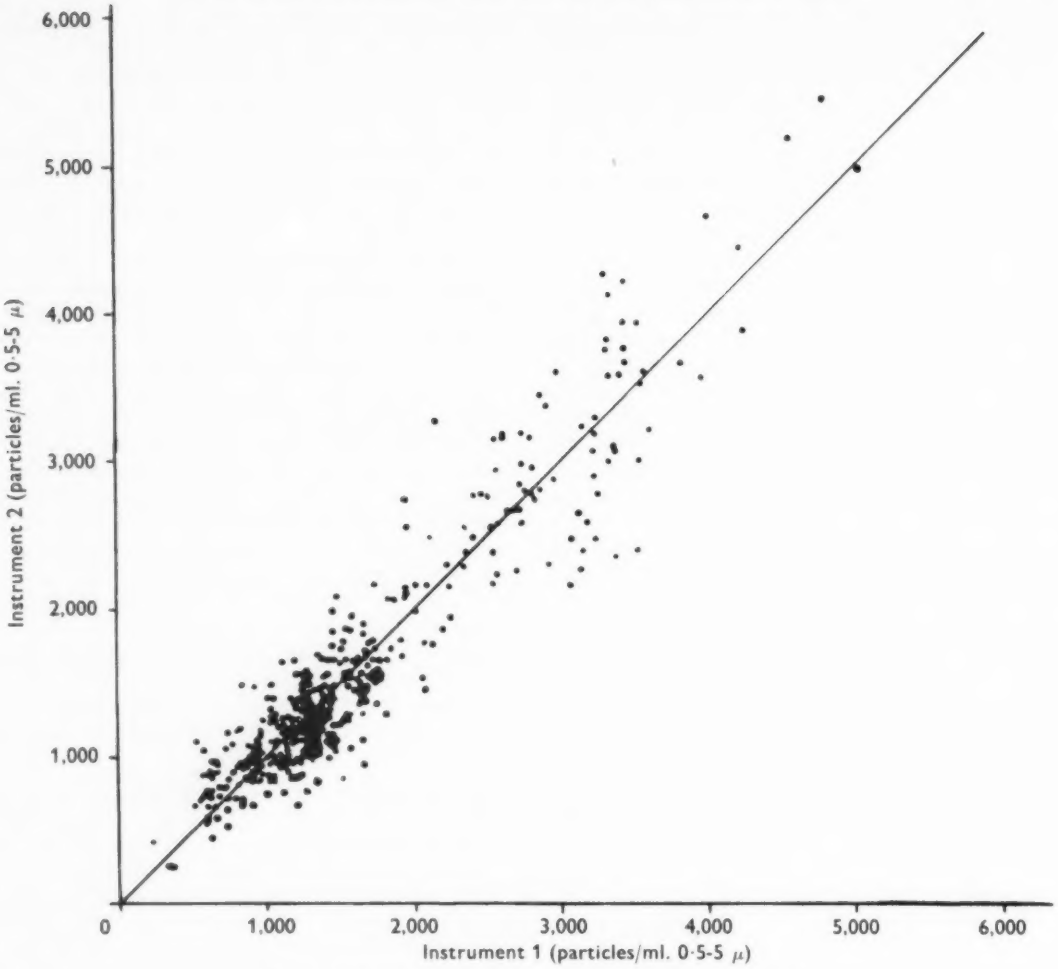


FIG. 9.—Airborne dust concentration using two thermal precipitators.

becomes the less likely is the effect to be important.

In the series illustrated in Fig. 9 there were 470 pairs of samples taken in a variety of collieries. The two instruments were operated by different observers. The samples were then coded and each was counted independently by three different observers, care being taken to ensure that the two samples of each pair were widely separated in the list of samples. Each observer made only one count of each deposit. Steps were taken to conceal the purpose of the trial from the observers until all the results were brought together.

The results illustrated show the scatter about the line of perfect agreement. From such pairs of results we can estimate the error of a measurement of the dust concentration made with the thermal precipitator. The results expressed in terms of the standard deviation about the mean are given in Table I. It can be seen that there is a tendency for a lower standard error, in percentage terms, the higher the concentration, although in general we may expect to find a standard error of about 15%. Beadle and Kerrich (1955), sampling in gold mines in South Africa and counting all the particles that could be seen after igniting the slides to remove carbon, found in a similar experiment that the standard error of a single sample was 13%. Burdekin and Dawes (1956), reporting on a comparison of two thermal precipitators, found a standard error of a single observation of about 25%.

Importance of Repeatability.—If the errors in measuring a concentration with the thermal precipitator were the only cause of variations in the results found in sampling in a colliery we would expect to

TABLE 1

ESTIMATES OF STANDARD ERROR OF A SINGLE MEASUREMENT OF DUST CONCENTRATION

Dust Concentration (particles/ml. 0·5-5μ)	Standard Error (% of dust concentration)
<750	18
750	16
1,250	12
1,750	10
2,250	14
2,750	12
>3,250	10

find the standard deviation of the concentrations to be about 15%, so that the standard deviation of the logarithms of the concentrations would be between 0·06 and 0·07 log particles per ml. In fact, as has been noted, the standard deviation found is 0·22 log particles per ml. when considering a single place during a single shift and 0·44 log particles per ml. when including all places and shifts. Thus, it can be seen that the errors of measurement, although quite large by some standards, have a negligible effect on the variability of the results obtained at different times and different places. In the past it has been recommended that enough particles should be counted to reduce the error of estimation of each sample to less than 5% (Watson, 1936; Transvaal Chamber of Mines, 1947). However, in practical work where it is desired to estimate the mean concentration at a particular place, or its variability, or the dust exposure of a worker or group of workers, the effort needed to achieve this precision is better spent in taking more samples. Large errors can be tolerated in the estimation of individual samples without appreciably affecting the precision of the mean concentration.

Systematic Errors

Overlapping.—The most important systematic error in thermal precipitator measurements is that due to overlapping amongst the particles deposited on the coverglasses. Particles covered by larger ones are not seen and since clumps or aggregates of particles are counted as single particles those aggregates formed by particles depositing near one another are also counted as single particles.

The bias in the count due to this overlapping increases with the density of the deposits and with the mean size of the particles (Roach, 1958). When sampling in a coal-mine Roach found that this bias amounted to 20% of the count at densities commonly used and recommended.

Contamination.—Another important source of bias is extraneous contamination of the coverglasses. They may become contaminated with dust while putting them into the thermal precipitator head and while taking them out. More contamination occurs if the plug holders and screw cap in the thermal precipitator head are not kept clean or if the screw cap is left off between samples. This leads to the number of particles deposited being overestimated. All particles less than 5 microns in diameter drawn into the thermal precipitator head are deposited on the coverglasses in a zone about 2 mm. wide (Green and Watson, 1935; Prewett and Walton, 1948), but when a deposit is examined under the microscope it is usually found that there is also a small amount of dust on the rest of the coverglass.

Fig. 10 illustrates the effect of this contamination on the density of the deposits. Two deposits were examined, one with little and the other with excessive contamination. The number of particles in unit area was determined at different points across the deposits. It can be seen that with the contaminated deposit (Fig. 10b) the edges of the deposit were ill-defined and there would have been considerable difficulty in determining how much of the dust was from the sample.

When excessive contamination is suspected it is our practice to examine the coverglass with a 16 mm. objective at a point away from the deposit and if it is found that there are more than 50 particles per sq. mm. the sample is rejected. To minimize the effect of contamination on the count the length of the traverse made across the sample is limited so as to span the sample dust and no further.

An example of the combined effect of the bias due to overlapping and contamination which normally occurs is illustrated in Fig. 11. This gives the expected errors for the count 0·5 to 5 microns for samples of dust of the kind obtained at a colliery. The continuous line gives the relationship between the number of particles counted and its expected bias. When the number counted is very high the number deposited is seriously underestimated, due to the large amount of overlapping whereas when the number counted is very low the extraneous contamination is a relatively large proportion of the count and the count is biased high. The dotted curves are the 95% confidence limits of the true mean plotted against the corresponding value of the mean.

Other Errors.—In addition to the biases from overlapping and contamination, which are inherent in the instrument, there are other biases which are more easily avoided. For example, the technician may tend to read the volume of each sample systematically high or low or the observer assessing the samples may consistently underestimate or overestimate the size of the particles. These biases are corrected as far as possible when training the technicians.

The measuring cylinder used in the sampling may not be accurate. Errors are reduced by using

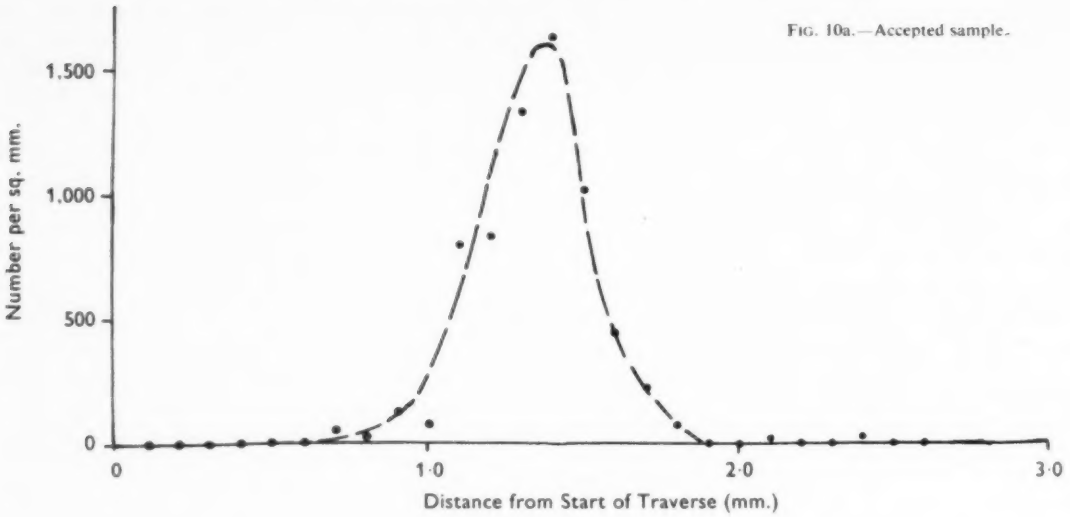


FIG. 10a.—Accepted sample.

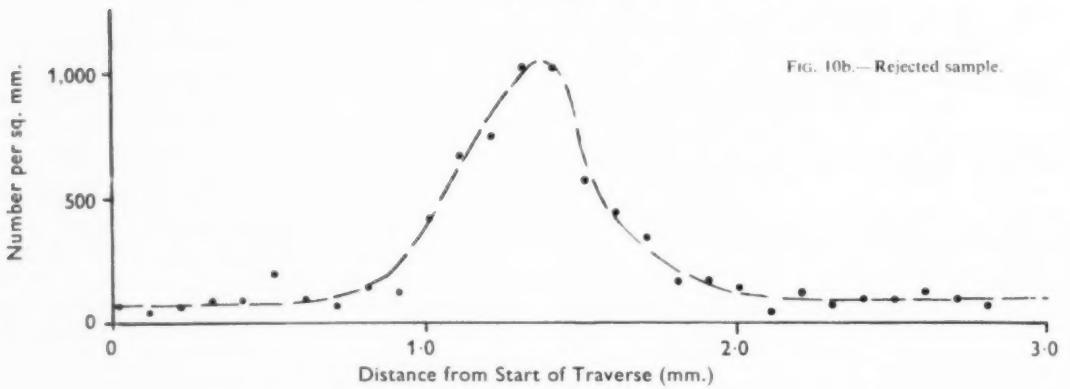


FIG. 10b.—Rejected sample.

FIG. 10.—The density of a deposit at points across it.

cylinders made to British Standard Specification 604. A 50 ml. cylinder of this kind will not be in error by more than 0·5 ml. at any point on the scale. Ten such cylinders were compared with an accurate burette and none was found with an error of more than 0·2 ml. at any point on the scale. On the other hand when six cylinders were tested which had no such guarantee of accuracy, it was found that at 20 ml. they were in error by between 0·6 and 1·2 ml.

The Time Factor

In determining the dust exposure of a group of workers their duration of exposure is measured as well as the average concentration to which they are exposed. This is done to derive an index of the amount of dust retained in the lungs.

It has been found by field studies that in all diseases due to accumulations of dust in the lungs the greatest incidence of pneumoconiosis occurs amongst men who have been exposed for the longest time to the highest concentration (Sayers, Bloomfield, Dallavalle, Jones, Dreessen, Brundage, and Britten, 1935; Dreessen, Dallavalle, Edwards, Miller, Sayers, Easom, and Trice, 1938; Flinn, Dreessen, Edwards, Riley, Bloomfield, Sayers, Cadden, and Rothman, 1939; Dreessen, Dallavalle, Edwards, Sayers, Easom, and Trice, 1940; Flinn, Seifert, Brinton, Jones, and Franks, 1941; Dreessen, Page, Hough, Trasko, Jones, and Franks, 1942; Bedford and Warner, 1943; Roach, 1953). Since men with pneumoconiosis have more dust in their lungs than others (Gough, 1947; King, Maguire, and Nagelschmidt, 1956) the logical conclusion is that the dust accumulates gradually in the lungs over a period of many years.

In the absence of evidence to the contrary, it seems likely that over the working range the rate of accumulation of the dust is simply proportional to

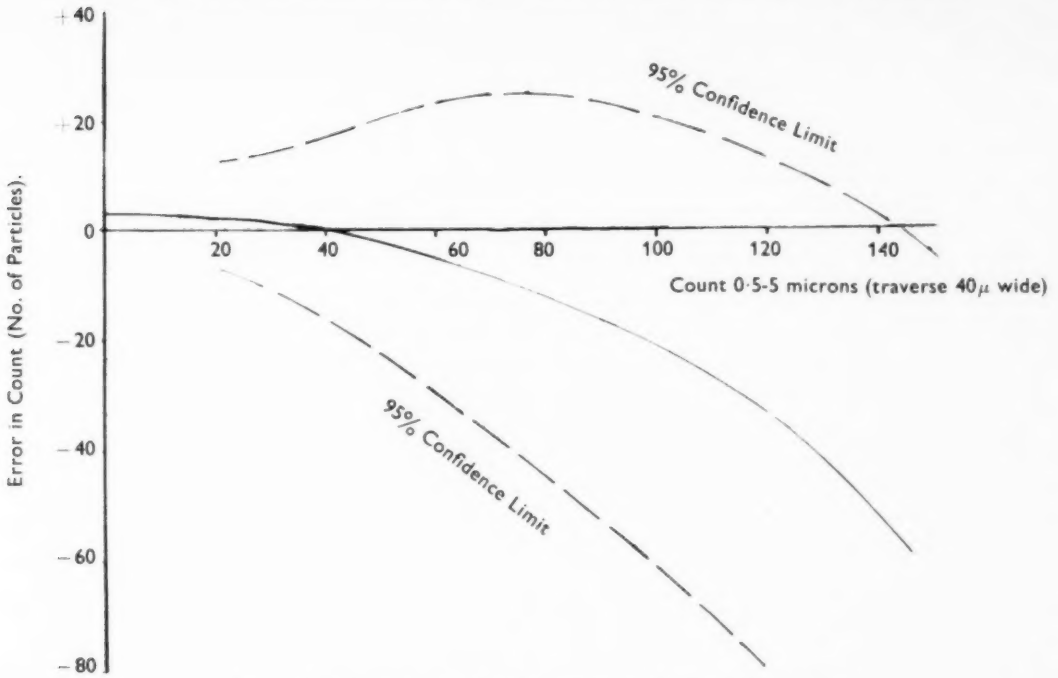


FIG. 11.—Bias due to overlapping and contamination related to density of deposit.

the concentration of dust inhaled (Wright, 1953). Consequently, the product of average concentration and duration of exposure is probably a good index of the dose of dust permanently retained in a man's lungs. The average concentration of particles between 0·5 and 5 microns is measured with the thermal precipitator and the duration of exposure in hours is measured by a simple time study done at the same time. The product of the two gives the dust exposure in particle-hours per ml. between 0·5 and 5 microns, or "particle-hours", for short.

Sampling Procedures

When measuring the dust exposure of groups of workers the samples are taken as close to the workers as practicable. To get the greatest possible coverage with the least number of samples each sample should be taken alongside a different worker. However, it is sometimes difficult to get from one worker to another and a series of samples may be taken alongside one worker before proceeding to the next. It may be necessary to stay with one worker for a whole shift, in which case a different worker is chosen each day. Whatever sampling procedure is adopted, the workers sampled on a particular shift are chosen at random from the population in order to obtain an unbiased estimate of their average dust exposure.

In control sampling where the primary purpose is to check that conditions have not deteriorated, sampling procedures have been developed based on measuring the dustiness at fixed positions, at times of maximum dustiness and in the dustiest positions, so that an ample safeguard is given that the average levels are below the level measured. These procedures are simple and practical but they are of little use for precise measurement of the average dust exposure of the men or how the dust exposure varies from one man to another (Oldham and Roach, 1952).

A Survey in a Colliery

The Sampling Procedure.—The object of this survey was to test the sampling procedure and practicability of measuring the dust exposure of coal-miners over a long period. For the purposes of the survey their dust exposure was considered to begin when they entered the cage which takes them underground and to cease when they left the cage again at the end of the day's work.

Colliers often arrive early or work overtime and the men at this colliery took from 20 minutes to two hours to travel between the pit bottom and their place of work.

A sampling procedure was therefore tried in which the technician was provided each day with a

list of six coal-getters chosen at random from the whole population. The technician went underground with one of these men and travelled with him to his place of work, taking samples on the way. He then travelled from one collier to the next at hourly intervals during the main part of the shift, from 8 a.m. to 2 p.m., and came out of the pit with the last collier on his list.

With this procedure each technician was able to take samples alongside 30 different colliers each week, but he had to be willing and able to travel considerable distances underground each day. It is necessary in this work to leave the technicians unsupervised for most of their work so that it is essential for reliable results that their task be light and simple.

The next method tried was to treat the men in each district of the colliery as a separate population so that the technician had to travel only over a limited area each day. This procedure was found to be an improvement, but only at the expense of added complications in the book-keeping as it became necessary to keep week-by-week records of the placing of the men in the different districts. The difficulties of keeping a tally on the jobs the men actually do over an extended period are considerable. For instance, over a year it was found that of 234 men who were visited, 79 (34%) were doing a different job from the one allocated to them in the colliery books.

The procedure finally adopted was that described by Oldham and Roach (1952). Each shift a technician went underground with a collier chosen at random from the whole population, stayed with him for the whole of the shift, and returned to the surface with him. This was the simplest and least laborious of the methods tried.

A list of the men employed on the underground staff was obtained from the colliery. The men were met at the start of their shift at the lamp room on the surface and accompanied underground. The job they did during the shift and where they worked was noted by the technicians so that the dust exposure associated with a particular type of job or district could be assessed at the end of the survey. If a collier was absent his dust exposure on that day was recorded as zero and the technician did not go underground. Samples were normally taken one after the other throughout the shift, but if the concentration was expected to be high, short-period samples of fixed duration were taken at intervals of 20 minutes, beginning at a time chosen at random within the first 20 minutes.

The survey lasted 55 weeks including a break of two weeks for the colliery summer holidays. The names of the men on the books at the start of the survey were placed in a random order and they were dealt with serially. During the survey it was found that of the 377 men selected, 49 (13%) were no longer employed at the colliery. Of the remaining 328, still employed, 109 were absent (33%) on the days when their dust exposure was to be estimated. A collier was not informed beforehand that he was due for a visit by the technician so that his attendance or otherwise was not affected. It has been found that when a worker is asked beforehand if he expects to be at work a few days ahead, he will often make a special effort to turn up and this may bias the estimation of his dust exposure.

Variability of the Dustiness.—The frequency distribution of the dust concentrations shown by the 2,725 samples obtained is illustrated in Fig. 12. The arithmetic mean was 288·7 particles per ml. The dots

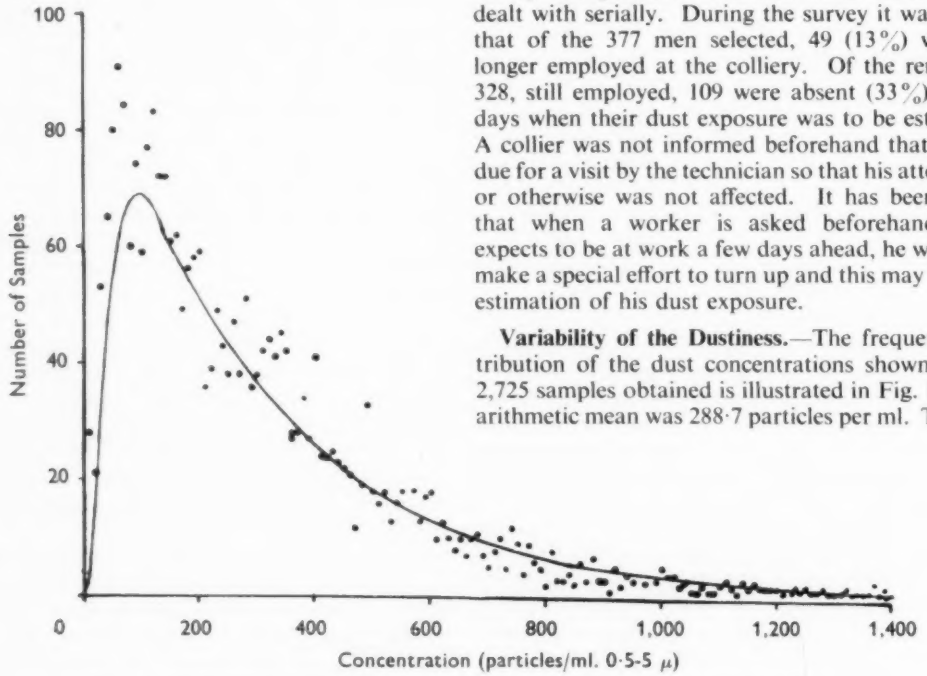


FIG. 12.—The frequency of occurrence of concentrations measured with the thermal precipitator.

TABLE 2
TIME SPENT AT WORK ON DIFFERENT SHIFTS

Time Underground (hours)	Name of Shift				Total
	Days (6.30 a.m.-2.00 p.m.)	Overlapping (8.30 a.m.-4.00 p.m.)	Afternoons (2.30 p.m.-10.00 p.m.)	Nights (10.30 p.m.-6.00 a.m.)	
<5·5	3	1	—	2	6
5·5<	1	—	—	—	1
6·0—	1	—	—	—	1
6·5—	3	—	—	—	3
7·0—	11	16	9	10	46
7·5—	89	4	17	36	146
8·0—	4	—	1	2	7
8·5—	2	—	—	—	2
>9·0—	6	—	—	1	7
Total	120	21	27	51	219
Mean (hr.)	7·58	7·27	7·58	7·44	7·52

in the diagram refer to the number of results at that particular level of concentration and the continuous line is a frequency distribution curve fitted to these frequencies on the assumption that the parent distribution is of log normal form. The standard deviation was 0·44 log particles per ml. The continuous curve describes the distribution well.

The highest concentration recorded in the survey was 6,190 particles per ml., more than 20 times the mean, and there were eight samples which showed concentrations more than 10 times the mean. On the other hand there were 28 samples for which the concentration was so low (less than 5 particles per ml.) that the dust on the sample was too sparse to count.

Duration of Exposure.—The colliers were supposed to spend seven and a half hours underground each shift. However, colliers who become ill or have an accident and those who need to come out to mend or get a piece of equipment may leave the mine before the end of the shift. Some men also work overtime. There is thus a considerable variation in the duration of exposure, illustrated by the summary given in Table 2. The shortest time spent underground was 0·8 hours and the longest 9·5 hours. The average time spent underground was 7·52 hours.

Time studies were done to measure the time spent travelling to and from the place of work, and on half the days the time spent working and resting between spells of work was also measured. In a number of jobs the work is machine minding, particularly those connected with the transport of trucks and roof supports between the pit bottom and the coal-face. In these jobs the observer could not distinguish clearly between the working and resting periods. This type of job was done on 19 days out of the 110 when detailed time studies were attempted.

The time spent in these different activities varied considerably as is illustrated by the results given in Table 3. The mean time spent working, during which the greatest dust exposure occurs, was 4.32 hours; the mean times spent travelling and resting were respectively 1·34 hours and 1·82 hours. On at least 10% of occasions the length of these periods was either less than half of the mean or more than one and a half times the mean.

TABLE 3
TIME OCCUPIED IN WORKING, TRAVELLING, AND RESTING ON DIFFERENT DAYS

Time Occupied (hours)	Activity		
	Working	Travelling	Resting
	Number of Days		
<0·5—	—	7	5
0·5—	1	56	12
1·0—	2	68	25
1·5—	2	50	17
2·0—	4	12	12
2·5—	6	2	5
3·0—	11	1	3
3·5—	5	1	9
4·0—	9	—	3
4·5—	20	—	—
5·0—	21	—	—
5·5—	3	—	—
>6·0—	7	—	—
Total	91	197	91
Mean (hr.)	4·32	1·34	1·82

Dust Exposure in Particle-hours.—On three occasions the colliers chosen, although usually employed underground, were sent to work on the surface clearing away a stock of coal. Their dust exposures were 290, 280, and 30 particle-hours. Excluding these figures, we give in Table 4 the mean dust exposures for each month. The number of shifts sampled each month varied because of annual leave and sickness absences in the colliery and among the sampling staff. There seems to be no steady trend either upwards or downwards in the dust exposure per shift over the period covered. However, the dust exposure per shift did vary a great deal. The minimum was 70 particle-hours per shift and the maximum was 17,090 particle-hours per shift, representing a range of more than 200-fold in the dust exposure. The mean dust exposure of all the

TABLE 4
MEAN DUST EXPOSURE IN PARTICLE-HOURS PER SHIFT OF ALL THOSE WORKING UNDERGROUND

Month	No. of Shifts Sampled	Mean Dust Exposure (particle-hours/shift)	Range of Observations	
			Minimum	Maximum
1	3	1,100	870	1,440
2	17	1,660	280	3,500
3	27	2,230	210	17,090
4	12	1,150	80	5,000
5	15	1,880	150	3,900
6	16	2,390	650	6,310
7	5	1,730	400	2,670
8	5	1,390	860	2,430
9	5	1,160	690	2,150
10	22	1,630	270	3,380
11	19	1,430	130	5,200
12	18	920	80	3,690
13	9	640	140	3,180
14	28	1,330	70	4,980
Mean of all shifts		1,549		

TABLE 5
DUST EXPOSURE IN DIFFERENT OCCUPATIONAL GROUPS

Dust Exposure (particle-hours per shift)	Number of Shifts			
	Coal-getters	Stone Workers	Others	All Underground
<500 –	1	12	38	51
500 –	2	10	29	41
1,000 –	4	6	16	26
1,500 –	4	8	11	23
2,000 –	12	2	4	18
2,500 –	11	1	3	15
3,000 –	8	2	3	13
3,500 –	2	0	2	4
4,000 –	2	2	0	4
4,500 –	1	0	1	2
5,000 –	2	0	0	2
5,500 –	0	0	0	0
6,000 –	0	1	0	1
>6,500	1	0	0	1
Mean	2,860	1,370	1,010	1,550

shifts sampled was 1,549 particle-hours per shift.

There is a very great variety of occupations underground and to study each of them thoroughly would take considerably longer than a year. The results are divided into three groups. The first includes coal-getters and their assistants, that is, the men who dig the coal and shovel it on to the conveyors; the second includes all the rippers, repairers, packers, and their assistants, that is, the men who work on stone; and the third group includes all the other workers such as labourers, transport workers, and specialists of various kinds who together account for about half the underground population.

The results of the measurements in these three occupational groups are shown in Table 5. The dustiest occupation is that of the coal-getters for whom the mean dust exposure was 2,860 particle-hours per shift. In the dustiest shift the collier's dust exposure was 17,090 particle-hours, the highest recorded. He was working in a rib end (a short extension of the face beyond the junction where it meets the return airway of the face) where the ventilation was very poor. The dust he produced while digging the coal would normally be swept away by the ventilation current, but on this occasion remained in the relatively stagnant air around him and led to his having a very high dust exposure.

Stone work was a less dusty occupation than that of coal-getting. The mean dust exposure per shift for the stone workers was 1,370 particle-hours. A dust exposure of 2,250 particle-hours per shift was exceeded in seven shifts out of 44. On six out of these seven occasions the man was working at the ripping lip in the return roadway of one of the faces during the coal-getting shift, whereas out of the remaining 37 occasions only three were spent at the return end during the coal-getting shift. The return ends of longwall faces are usually the most dusty places during the coal-getting shift as the airborne dust made by all the coal-getters along the face is drawn by the ventilation current to the return end.

The remaining occupational group under "others" in Table 5 had a lower dust exposure per shift worked than either the coal-getters or the stone workers. Their mean dust exposure was 1,010 particle-hours per shift. This group included a large number working on the night and afternoon shifts, when no coal-getting was in progress and others who worked some distance from the coalface.

Variations in Dustiness along the Face.—That the dustiness is greatest at return ends is illustrated by the results for the coal-getters. During the survey a note was always made of where the men were working and for the coal-getters the distance to the main intake road to the face was recorded. The mean concentrations at these different positions are summarized in Table 6. They exclude the dust measurements made while travelling to and from work and while resting during the mid-shift break. The dustiness was greatest towards the return end although the increase is not as great as might be expected. Some dust enters the face with the intake air. Also on some faces there is in addition to the main intake air, a further, although much smaller, supply of air half-way along from the loader gate. Another complicating factor is that the coalface itself, although bounded on three sides by solid rock, namely, the roof, floor, and coal itself, is bounded on the fourth side by a series of stone packs at right angles to the face between which the roof is allowed to fall and there is some leakage of air through this loosely packed material which only partially mixes with the air passing the colliers.

Fig. 13 illustrates the results of a survey at another colliery with a more simple layout of the faces where there is a much clearer demonstration of the increase of dustiness towards the return end.

In general, the more complicated the ventilation

TABLE 6
DUST CONCENTRATION ON LONGWALL FACES DURING THE COAL-GETTING SHIFT

Distance from Intake Road (yards)	Mean Concentration (particles/ml. 0·5 to 5 microns)	Number of Shifts Included
<20	280	6
20–	340	7
40–	390	6
60–	340	7
80–	420	4
100–	400	8
120–	390	11
140–	720	2
160–	490	2
180–	—	—
>200	500	1

The results from 54 shifts are shown, four more than in Table 5 for coal-getters, due to the inclusion of shifts where the travelling dust exposure was not known and the exclusion of shifts where the collier did not work on a longwall face and where the collier worked in the rib end.

system, the more dust entering with the intake air and the wider the face, the more difficult is it to detect the increase in dustiness along the length of the face.

A Survey in a Steel Works

Object of the Survey.—In the melting shop of a large steel works employing about 10,000 people there were 16 smelting furnaces. These furnaces deteriorate with use and are then partially or completely dismantled and rebuilt. There were complaints from the men doing this work that their job was particularly dusty.

A survey was made of the dust exposure of these

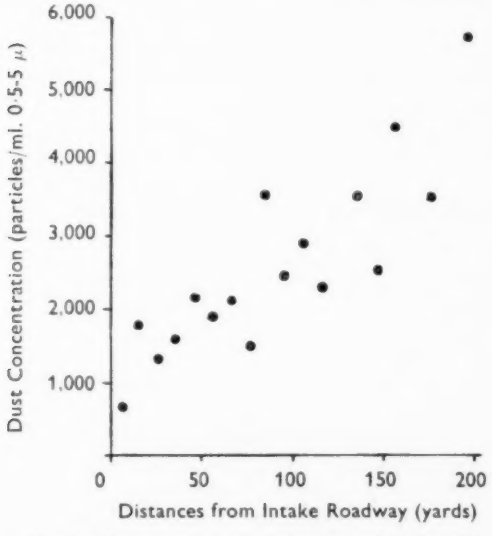


FIG. 13.—The dust concentration during the coal-getting shift on the coal-face at a colliery.

Note: Each point represents the average concentration during the whole shift. In all, 1,267 samples were taken, spread over 149 shifts.

furnace dismantlers and repairers and of other groups working in the bar and strip mills where it was expected there would be little or no dust.

The men in each of the occupational groups worked within 400 yards of one another and it was practicable to get from one to another within 10 minutes. It was therefore possible in this instance to adopt the more efficient sampling procedure of moving from worker to worker between successive samples.

Method of Sampling.—Names were chosen at random from a works list of the men employed in different occupations and samples were taken alongside each of these men using the standard thermal precipitator (Fig. 1a). For each sample the tripod was placed as close as possible to the worker without interfering with his work. As soon as the apparatus had been set up a sample of 10 minutes' duration was taken and then the sampler moved on to the next man on the list. In order to cover as many workers as possible only a short time was spent with each one, just sufficient to take one sample. It was found that it took about 20 minutes to complete each sample. The duration of exposure began when the workers clocked in and finished when they clocked out. Since they all clocked in and out within a few minutes of each other their durations of exposure were effectively equal. The survey lasted three weeks.

Results.—The mean concentrations of dust of all sizes are shown in Table 7. The samples were counted for total number of particles using a 2 mm. oil-immersion objective in the microscope. Particles as small as 0·1 microns diameter can be seen with this arrangement. In all three of the occupational groups the mean concentration was very high but of the three groups it was the bar mill workers who were exposed to the highest concentration and not, as was expected, the bricklayers.

The Source of the Dust.—It seemed possible that the dust in the bar mill came from the smoke from the pre-heating furnace. At the time of the sampling a note was made of where in the mill the particular worker was working. We could thus determine where in the mill the highest concentration existed. Table 8 gives the results, showing that there is no clear trend of dustiness along the length of the mill. This finding and also the finding that the mill as a whole was more dusty than the steel melting shop suggested that very little of the airborne dust in the works came from the demolition and building operations.

It was concluded that probably most of the dust came from outside and entered with the ventilating air. Further, it was found that the dust in the samples was very fine, as would be expected if it was

TABLE 7

MEAN NUMBER OF PARTICLES PER MILLILITRE OF ALL SIZES AT THE STEEL WORKS VISIBLE UNDER THE OPTICAL MICROSCOPE

Occupational Group	Number of Samples Taken	Mean Concentration (particles/ml.)
Bricklayers ("dusty")	67	7,220
Bar mill ("non-dusty")	42	16,830
Strip mill ("non-dusty")	62	6,800

the normal atmospheric pollution of the neighbourhood. The fineness of the dust is illustrated in Table 9 where the diameter at the median projected area is given for 20 samples chosen at random from all the samples taken and compared with samples from 20 collieries. The mean size at the steel works was 0·77 microns and in the collieries was 10·5 microns.

TABLE 8

MEAN CONCENTRATION AT DIFFERENT POSITIONS IN THE BAR MILL

Distance from Furnace (yards)	Number of Samples Taken	Mean Concentration (particles/ml., all sizes)
0-100	14	15,550
100-200	14	27,170
200-300	10	6,890
300-420	4	10,050

Measurements made of the dust concentrations in the air entering the works confirmed that high concentrations of fine dust were entering from outside. Samples were taken around the works on the windward side. The results ranged from 6,000 to 39,000 particles/ml. and the average concentration was 16,860 particles/ml. The dust was again very fine. The dust, or smoke, appeared to come in part from bonfires of rubbish in the yards and from the smoke of the steam locos working in the large shunting yards behind the works.

TABLE 9

MEAN SIZE OF DUST IN 20 SAMPLES FROM STEEL WORKS AND IN SAMPLES FROM COALFACE AT 20 DIFFERENT COLLIERIES

Steel Works		Collieries	
Median Diameter in Microns	No. of Samples	Median Diameter in Microns	No. of Samples
<0·3	0	<3·0	0
0·3–	3	3·0–	2
0·5–	4	6·0–	7
0·7–	6	9·0–	4
0·9–	3	12·0–	5
1·1–	2	15·0–	0
1·3–	2	18·0–	2
>1·5	0	>21·0	0
Total	20	Total	20
Overall mean: 0·77 microns		Overall mean: 10·5 microns	

The area median diameter is given, that is, the size at which the total projected area of all larger particles is equal to the total projected area of all smaller particles.

Chest radiographs were taken of the men and a summary of the readings for the furnace dismantlers and repairers is given in Table 10. All those who had had two or more years' experience in mine or factory, other than at the steel works, were rejected from the analysis. It can be seen that about 8% of the men were classified as category 1 or more. The prevalence of such radiological abnormalities in 12 British collieries was given by Cochrane, Davies, Chapman, Rae, Rinsler, and Williams (1956) and in these the prevalence ranged from 18% to 62%. Thus, the risk of pneumoconiosis at the steel works must be relatively low. Presumably the particles were so small that, despite their large numbers, the total weight of dust retained in the workers' lungs was comparatively low.

TABLE 10

PREVALENCE OF PNEUMOCONIOSIS IN FURNACE DISMANTLERS AND REPAIRERS (P.R.U. CLASSIFICATION)

Category of Radiograph	No. of Men	% of Men
0	149	92
1	10	6
2	2	1
3	1	1
Total	162	100

The mean period of exposure was 11·7 years, varying from one month to 33 years.

However, the dismantlers maintained that theirs was a very dusty job and the worst dust conditions occurred when they were breaking down the roof of a furnace. Samples were therefore taken to cover the period when a roof was being broken down. The results are given in Table 11.

TABLE 11

DUST CONCENTRATIONS WHEN BREAKING DOWN ROOF OF A FURNACE

Sample	Activity	Number of Particles per ml. with Diameter in Microns		
		<0·5	0·5 to 5·0	>5·0
1	None	42,200	5,450	0
2	Dismantling	26,300	5,230	0
3	Dismantling	53,800	7,660	60
4	None	30,400	4,970	0

Samples 1 and 4 were taken immediately before and after the operation. During the second and third sample the roof was being broken in. Since it could be seen that the billowing cloud of dust was not reaching the thermal precipitator during sample 2, the instrument was put inside the furnace for sample 3, just outside the range of the falling brickwork. This sample gave 60 particles larger than 5

microns in diameter per ml. where none were found in the other samples. Assuming these particles were collected only when the heavy cloud of dust enveloped the instrument as the roof fell in, a period of six seconds, then since the sample lasted 10 minutes, 100 times as long, the peak concentration of this coarse dust was of the order of 60 × 100, that is, 6,000 particles per ml. Thus, when a roof is broken down a spectacular cloud of coarse dust is produced but it lasts for a few seconds only.

This operation and similar ones no doubt gave rise to the belief amongst dismantlers that they were exposed to a particularly high risk of pneumoconiosis.

Discussion

The thermal precipitator is widely used at the present time. It is fairly reliable, although not very accurate. Because of the high variability of the dustiness existing in industrial areas a high precision can only be obtained with it by taking large numbers of samples. At the same time it is necessary to employ an experienced technician both to operate the instrument and to count and measure the size of the dust in the samples. Consequently, in practice the precision achieved in a survey using this instrument is limited by the amount of time and money available for technicians to take and assess the samples. Taking into account wages, expenses, the cost of materials, and the wear and tear on the instruments, the total cost of such a survey is usually found to lie between £1 and £2 per sample taken.

Much of the expense of these surveys is due to the time spent taking the large numbers of samples needed to cover the wide fluctuations in dustiness from time to time. Consequently, instrument development at the present time is directed to producing instruments which will run unattended for long periods and give readings of the average concentration over the whole of the run. Instruments such as the long-running thermal precipitator (Hamilton, 1956), the drum pump sampler (Lloyd, Winder, and Gillard, 1951), the liquid trap sampler (Barker, O'Connor, and Winder, 1954), and the automatic sedimentation cell (Davies, 1954) are examples of these.

Where the time of exposure is very variable its measurement must be given as much attention as the measurement of concentration. This is particularly important in collieries. It has been shown in an earlier paper (Roach, 1954) that not only do colliers vary amongst themselves but also the duration of exposure of colliers in different collieries is markedly different; this is an additional reason for making careful measurements when comparing one colliery with another.

In surveys of dust exposure the samples are taken alongside selected individuals and the first few workers often have some misgivings that they should be picked out from their fellows in connexion with a study of a disease about which they know very little. Such fears are allayed when it is explained how a particular worker comes to be chosen and the men are soon reassured when they see the sampler taking samples alongside their fellow workers. In practice, it is found that wage-earners lose interest in the conduct of these surveys after a few days. This lack of interest is not discouraged since it is essential that the workers' habits are not altered by the sampling.

The procedure used has to be sufficiently simple to be performed by the field survey personnel under the distracting conditions met with in industry and at the same time has to yield unbiased and accurate estimates of concentration and duration of exposure. This is most simply done by choosing a representative group of men from a works list with the aid of random sampling numbers and taking the dust samples alongside each in turn. A sample of the population consisting of the first few names given in a works list, the first few names in a list in order of works number, or in alphabetical order is often unreliable. With the first two of these we have found that the men are then placed in order to some extent according to seniority, so that selection of the first few men does not give a representative sample, and in the last it was found that foreign names were more commonly found in the last few letters of the alphabet. Foreign workers seem to be placed in particular jobs or are placed together because of language difficulties, so that sampling, for example, only those men whose names begin with a letter in the upper half of the alphabet would have given a biased sample.

This sampling procedure may be modified in several ways so as to give a higher accuracy in the averages for the same number of samples taken. For instance, extra samples can be taken in conditions where the dustiness is likely to be excessive or particularly variable. Similarly, for sampling in order to check on the control of dustiness by dust prevention and suppression devices, more samples can be taken in places where the dustiness is near the upper permissible level than those which are much less dusty. Control chart techniques are likely to be used to help do this systematically (Tomlinson, 1957). Another way in which control sampling can be improved is by measuring the dust exposure of the men rather than relying solely on measuring the dust concentration at a fixed place.

The assessment of airborne dust samples is often done by counting the particles by eye under the microscope. No matter how much the procedure is

TABLE 7

MEAN NUMBER OF PARTICLES PER MILLILITRE OF ALL SIZES AT THE STEEL WORKS VISIBLE UNDER THE OPTICAL MICROSCOPE

Occupational Group	Number of Samples Taken	Mean Concentration (particles/ml.)
Bricklayers ("dusty")	67	7,220
Bar mill ("non-dusty")	42	16,830
Strip mill ("non-dusty")	62	6,800

the normal atmospheric pollution of the neighbourhood. The fineness of the dust is illustrated in Table 9 where the diameter at the median projected area is given for 20 samples chosen at random from all the samples taken and compared with samples from 20 collieries. The mean size at the steel works was 0·77 microns and in the collieries was 10·5 microns.

TABLE 8

MEAN CONCENTRATION AT DIFFERENT POSITIONS IN THE BAR MILL

Distance from Furnace (yards)	Number of Samples Taken	Mean Concentration (particles/ml., all sizes)
0-100	14	15,550
100-200	14	27,170
200-300	10	6,890
300-420	4	10,050

Measurements made of the dust concentrations in the air entering the works confirmed that high concentrations of fine dust were entering from outside. Samples were taken around the works on the windward side. The results ranged from 6,000 to 39,000 particles/ml. and the average concentration was 16,860 particles/ml. The dust was again very fine. The dust, or smoke, appeared to come in part from bonfires of rubbish in the yards and from the smoke of the steam locos working in the large shunting yards behind the works.

TABLE 9

MEAN SIZE OF DUST IN 20 SAMPLES FROM STEEL WORKS AND IN SAMPLES FROM COALFACE AT 20 DIFFERENT COLLIERIES

Steel Works		Collieries	
Median Diameter in Microns	No. of Samples	Median Diameter in Microns	No. of Samples
<0·3	0	<3·0	0
0·3–	3	3·0–	2
0·5–	4	6·0–	7
0·7–	6	9·0–	4
0·9–	3	12·0–	5
1·1–	2	15·0–	0
1·3–	2	18·0–	2
>1·5	0	>21·0	0
Total	20	Total	20
Overall mean: 0·77 microns		Overall mean: 10·5 microns	

The area median diameter is given, that is, the size at which the total projected area of all larger particles is equal to the total projected area of all smaller particles.

Chest radiographs were taken of the men and a summary of the readings for the furnace dismantlers and repairers is given in Table 10. All those who had had two or more years' experience in mine or factory, other than at the steel works, were rejected from the analysis. It can be seen that about 8% of the men were classified as category 1 or more. The prevalence of such radiological abnormalities in 12 British collieries was given by Cochrane, Davies, Chapman, Rae, Rinsler, and Williams (1956) and in these the prevalence ranged from 18% to 62%. Thus, the risk of pneumoconiosis at the steel works must be relatively low. Presumably the particles were so small that, despite their large numbers, the total weight of dust retained in the workers' lungs was comparatively low.

TABLE 10

PREVALENCE OF PNEUMOCONIOSIS IN FURNACE DISMANTLERS AND REPAIRERS (P.R.U. CLASSIFICATION)

Category of Radiograph	No. of Men	% of Men
0	149	92
1	10	6
2	2	1
3	1	1
Total	162	100

The mean period of exposure was 11·7 years, varying from one month to 33 years.

However, the dismantlers maintained that theirs was a very dusty job and the worst dust conditions occurred when they were breaking down the roof of a furnace. Samples were therefore taken to cover the period when a roof was being broken down. The results are given in Table 11.

TABLE 11

DUST CONCENTRATIONS WHEN BREAKING DOWN ROOF OF A FURNACE

Sample	Activity	Number of Particles per ml. with Diameter in Microns		
		<0·5	0·5 to 5·0	>5·0
1	None	42,200	5,450	0
2	Dismantling	26,300	5,230	0
3	Dismantling	53,800	7,660	60
4	None	30,400	4,970	0

Samples 1 and 4 were taken immediately before and after the operation. During the second and third sample the roof was being broken in. Since it could be seen that the billowing cloud of dust was not reaching the thermal precipitator during sample 2, the instrument was put inside the furnace for sample 3, just outside the range of the falling brickwork. This sample gave 60 particles larger than 5

microns in diameter per ml. where none were found in the other samples. Assuming these particles were collected only when the heavy cloud of dust enveloped the instrument as the roof fell in, a period of six seconds, then since the sample lasted 10 minutes, 100 times as long, the peak concentration of this coarse dust was of the order of 60 × 100, that is, 6,000 particles per ml. Thus, when a roof is broken down a spectacular cloud of coarse dust is produced but it lasts for a few seconds only.

This operation and similar ones no doubt gave rise to the belief amongst dismantlers that they were exposed to a particularly high risk of pneumoconiosis.

Discussion

The thermal precipitator is widely used at the present time. It is fairly reliable, although not very accurate. Because of the high variability of the dustiness existing in industrial areas a high precision can only be obtained with it by taking large numbers of samples. At the same time it is necessary to employ an experienced technician both to operate the instrument and to count and measure the size of the dust in the samples. Consequently, in practice the precision achieved in a survey using this instrument is limited by the amount of time and money available for technicians to take and assess the samples. Taking into account wages, expenses, the cost of materials, and the wear and tear on the instruments, the total cost of such a survey is usually found to lie between £1 and £2 per sample taken.

Much of the expense of these surveys is due to the time spent taking the large numbers of samples needed to cover the wide fluctuations in dustiness from time to time. Consequently, instrument development at the present time is directed to producing instruments which will run unattended for long periods and give readings of the average concentration over the whole of the run. Instruments such as the long-running thermal precipitator (Hamilton, 1956), the drum pump sampler (Lloyd, Winder, and Gillard, 1951), the liquid trap sampler (Barker, O'Connor, and Winder, 1954), and the automatic sedimentation cell (Davies, 1954) are examples of these.

Where the time of exposure is very variable its measurement must be given as much attention as the measurement of concentration. This is particularly important in collieries. It has been shown in an earlier paper (Roach, 1954) that not only do colliers vary amongst themselves but also the duration of exposure of colliers in different collieries is markedly different; this is an additional reason for making careful measurements when comparing one colliery with another.

In surveys of dust exposure the samples are taken alongside selected individuals and the first few workers often have some misgivings that they should be picked out from their fellows in connexion with a study of a disease about which they know very little. Such fears are allayed when it is explained how a particular worker comes to be chosen and the men are soon reassured when they see the sampler taking samples alongside their fellow workers. In practice, it is found that wage-earners lose interest in the conduct of these surveys after a few days. This lack of interest is not discouraged since it is essential that the workers' habits are not altered by the sampling.

The procedure used has to be sufficiently simple to be performed by the field survey personnel under the distracting conditions met with in industry and at the same time has to yield unbiased and accurate estimates of concentration and duration of exposure. This is most simply done by choosing a representative group of men from a works list with the aid of random sampling numbers and taking the dust samples alongside each in turn. A sample of the population consisting of the first few names given in a works list, the first few names in a list in order of works number, or in alphabetical order is often unreliable. With the first two of these we have found that the men are then placed in order to some extent according to seniority, so that selection of the first few men does not give a representative sample, and in the last it was found that foreign names were more commonly found in the last few letters of the alphabet. Foreign workers seem to be placed in particular jobs or are placed together because of language difficulties, so that sampling, for example, only those men whose names begin with a letter in the upper half of the alphabet would have given a biased sample.

This sampling procedure may be modified in several ways so as to give a higher accuracy in the averages for the same number of samples taken. For instance, extra samples can be taken in conditions where the dustiness is likely to be excessive or particularly variable. Similarly, for sampling in order to check on the control of dustiness by dust prevention and suppression devices, more samples can be taken in places where the dustiness is near the upper permissible level than those which are much less dusty. Control chart techniques are likely to be used to help do this systematically (Tomlinson, 1957). Another way in which control sampling can be improved is by measuring the dust exposure of the men rather than relying solely on measuring the dust concentration at a fixed place.

The assessment of airborne dust samples is often done by counting the particles by eye under the microscope. No matter how much the procedure is

simplified this is a tedious and time-consuming activity. It is hoped that automatic counting machines will be developed in the future to do the counting more rapidly, cheaply, and objectively (Walton, 1954).

Although the main features of pneumoconiosis are known, the relative importance of the various factors which influence the deposition and retention of dust and its effect on the lung is but vaguely understood. For example, the harder the men work the greater will be the rate of inhalation and the greater will be the proportion of dust caught in the upper respiratory tract, particularly of the larger sizes. At the same time, a greater volume of lung is used in breathing with the result that the dust deposited in the alveoli will be finer and more widespread. To investigate the importance of these particular factors it is likely that in field studies of pneumoconiosis measurements of respiratory ventilation will have to be taken in addition to measurements of dust exposure.

The practical problem of determining the relations between dust exposure and its effects on the men is beset by two major difficulties. First, since pneumoconiosis is the result of exposure to dust for 10 to 20 years, the prevalence of pneumoconiosis in a group of workers can be related to the dust conditions prevailing only if these conditions have remained unaltered for many years. Secondly, although breathlessness is associated with pneumoconiosis it is not known how much of the one is caused by the other. Both these difficulties can be overcome by field surveys which last for many years, tracing the dust exposure of the men from the time they enter the industry and measuring the progressive effect of the accumulations of dust with periodic medical examination (see, for example, Fay, 1957).

Thanks are due, first to my technicians, Messrs. B. P. Pryce, R. P. Pryce, W. J. Davies, R. D. Evans, and J. Williams, who took and assessed most of the dust samples.

On statistical aspects, Mr. P. D. Oldham gave much help and advice and Mr. R. G. Carpenter analysed some of the results. Many of the ideas and methods presented in this paper were developed in conversations with Mr. Oldham.

Dr. B. M. Wright was responsible for many ingenious features of the apparatus and Messrs. V. Gubb and F. Hyett also helped in this.

None of this work would have been possible without the cooperation of the managements and employees of the mines and steel works where the field work was undertaken.

Dr. R. S. F. Schilling, of the London School of Hygiene and Tropical Medicine, and Mr. J. R. Hodkinson, of the Safety in Mines Research Establishment, made many valuable suggestions in the preparation of this paper.

Finally, I would like to thank Dr. J. C. Gilson, Director of this Unit, and also Dr. A. L. Cochrane without whose continual encouragement this material would not have been published.

References

Barker, C. B., O'Connor, D. T., and Winder, G. E. (1954). Ministry of Fuel and Power Safety in Mines Research Establishment Res. Rep. No. 93.
Beadle, D. G., and Kerrich, J. E. (1955). *J. Chem. Metall. Ming Soc. S. Afr.*, **56**, 219.
Bedford, T., and Warner, C. G. (1943). *Spec. Rep. Scr., med. Res. Coun. (Lond.)*, No. 244.
——, —— (1950). *British J. industr. Med.*, **7**, 187.
Brown, C. E. (1931a). *J. industr. Hyg.*, **13**, 285.
—— (1931b). *Ibid.*, **13**, 293.
Brown, J. H., Cook, K. M., Ney, F. G., and Hatch, T. (1950). *Amer. J. publ. Hlth*, **40**, 450.
Burdekin, J. T., and Dawes, J. G. (1956). *Brit. J. industr. Med.*, **13**, 196.
Cartwright, J., and Nagelschmidt, G. (1951). Ministry of Fuel and Power Safety in Mines Research Establishment Res. Rep. No. 24.
Cochrane, A. L., Davies, I., Chapman, P. J., Rae, S., Rinsler, A. H., and Williams, M. C. H. (1956). *Brit. J. industr. Med.*, **13**, 231.
Davies, C. N. (1949). *Ibid.*, **6**, 245.
—— (1954). *Dust is Dangerous*, p. 24. Faber and Faber, London.
Dreessen, W. C., Dallavalle, J. M., Edwards, T. I., Miller, J. W., Sayers, R. R., Easom, H. F., and Trice, M. F. (1938). *Publ. Hlth Bull. (Wash.)*, No. 241.
——, ——, ——, Sayers, R. R., Easom, H. F., and Trice, M. F. (1940). *Ibid.*, No. 250.
——, Page, R. T., Hough, J. W., Trasko, V. M., Jones, J. L., and Franks, R. W. (1942). *Ibid.*, No. 277.
Fairs, G. L. (1943). *Chem. and Ind.*, **62**, 374.
Fay, J. W. J. (1957). *Nature (Lond.)*, **180**, 309.
Findeisen, W. (1935). *Pflüg. Arch. ges. Physiol.*, **236**, 367.
Flinn, R. H., Dreessen, W. C. Edwards, T. I., Riley, E. C., Bloomfield, J. J., Sayers, R. R., Cadden, J. F., and Rothman, S. C. (1939). *Publ. Hlth Bull. (Wash.)*, No. 244.
——, Seifert, H. E., Brinton, H. P., Jones, J. L., and Franks, R. W. (1941). *Ibid.*, No. 270.
Gessner, H., Rüttner, J. R., and Bühler, H. (1949). *Schweiz. med. Wschr.*, **79**, 1241.
Gough, J. (1947). *Occup. Med.*, **4**, 86.
Green, H. L., and Watson, H. H. (1935). *Spec. Rep. med. Res. Coun. (Lond.)*, No. 199.
Hamilton, R. J. (1956). *J. Sci. Instrum.*, **33**, 395.
——, Holdsworth, M. A., and Walton, W. H. (1954). *Brit. J. appl. Phys.*, **5**, S101.
Heywood, H. (1946). *Trans. Instn Ming and Metall.*, **55**, 391.
King, E. J., Maguire, B. A., and Nagelschmidt, G. (1956). *Brit. J. industr. Med.*, **13**, 9.
Landahl, H. D. (1950). *Bull Math. Biophys.*, **12**, 43.
——, and Herrmann, R. G. (1948). *J. industr. Hyg.*, **30**, 181.
——, Tracewell, T. N., and Lassen, W. H. (1951). *A.M.A. Arch. industr. Hyg.*, **3**, 359.
——, ——, —— (1952). *Ibid.*, **6**, 508.
Lloyd, H., Winder, G. E., and Gillard, D. A. (1951). Ministry of Fuel and Power Safety in Mines Research Establishment Res. Rep. No. 29.
May, K. R. (1945). *J. Sci. Instrum.*, **22**, 187.
Oldham, P. D. (1953). *Brit. J. industr. Med.*, **10**, 227.
——, and Roach, S. A. (1952). *Ibid.*, **9**, 112.
Owens, J. S. (1931). *Suspended Matter in Air*. In Lunge and Keane's *Technical Methods of Chemical Analysis*, 2nd ed., Vol. 3, pp. 601-659. Gurney and Jackson, London.
Patterson, H. S., and Cawood, W. (1936). *Trans. Faraday Soc.*, **32**, 1084.
Prewett, W. C., and Walton, W. H. (1948). Porton Technical Paper No. 63.
Roach, S. A. (1953). *Brit. J. industr. Med.*, **10**, 220.
—— (1954). *Ibid.*, **11**, 54.
—— (1958). *Ibid.*, **15**, 250.
Sayers, R. R., Bloomfield, J. J., Dallavalle, J. M., Jones, R. R., Dreessen, W. C., Brundage, D. K., and Britten, R. H. (1935). *Publ. Hlth Bull. (Wash.)*, No. 221.
Transvaal Chamber of Mines (1947). *Quality of Mine Air*. Johannesburg.
Tomlinson, R. C. (1957). *Applied Statistics*, **6**, 198.
Van Wijk, A. M., and Patterson, H. S. (1940). *J. industr. Hyg.*, **22**, 31.
Walton, W. H. (1954). *Brit. J. appl. Phys.*, **5**, S121. [Suppl.].
Watson, H. H. (1936). *Trans. Instn Ming and Metall.*, **46**, 176.
—— (1952). *Brit. J. industr. Med.*, **9**, 80.
——, and Mulford, D. F. (1954). *Brit. J. appl. Phys.*, **5**, S105.
Wilson, H. B., Sylvester, G. E., Laskin, S., LaBelle, C. W., and Stokinger, H. E. (1948). *J. industr. Hyg.*, **30**, 319.
Wilson, I. B., and LaMer, V. K. (1948). *Ibid.*, **30**, 265.
Wright, B. M. (1953). *Brit. J. industr. Med.*, **10**, 235.
—— (1954). *J. Sci. Instrum.*, **31**, 203.

Brit. J. industr. Med., 1959, **16**, 123.

PULMONARY FIBROSIS IN AN ALUMINIUM WORKER

BY

JOHN MITCHELL

From the Bolton Hospitals Group

(RECEIVED FOR PUBLICATION NOVEMBER 26, 1958)

Aluminium dust has never been shown to be harmful to man in Great Britain. This paper reports a fatal case of progressive pulmonary fibrosis in a young man occupationally exposed to a heavy concentration of fine aluminium dust. Clinically, radiologically, and pathologically this case was indistinguishable from cases of aluminium fibrosis of the lung described by Shaver in Canada.

In Great Britain there have been no reports of pulmonary fibrosis due to particulate aluminium. On the contrary, the Medical Research Council's Industrial Pulmonary Diseases Committee in 1936 investigated 50 workers exposed to aluminium dust and were unable to find any evidence that it caused fibrosis of the lung. Hunter, Milton, Perry, and Thompson (1944) studied the health and environment of 97 duralumin propeller grinders and concluded that there was no evidence that it occasioned any disease of the trachea, bronchi, or lungs. Eloquent testimony to its innocent reputation is the fact that coalminers have been deliberately exposed to this dust (*Lancet*, 1956) with the intention of preventing pneumoconiosis. On the other hand, in Germany (Goralewski, 1947) and Canada (Shaver, 1948) cases have occurred which have been recorded in a growing literature which has been summarized by Perry (1955).

Case History

A.G. died, aged 22.*

After leaving school he worked as an agricultural labourer until he was 19. At this age, in March, 1951, he joined a factory making fine aluminium powder and worked in an atmosphere heavily contaminated with fine aluminium dust until disabled by breathlessness in December, 1953. He gave no history of previous illness except that in November, 1951, he had been admitted to hospital for 10 days for treatment of second degree burns received at work. The breathlessness became progressively worse and by March, 1954, he had to walk slowly on the flat, though he was able to sleep comfortably with one pillow. Three months later the breathlessness was such that he spent most of the day in his bedroom; bouts of morning cough, producing occasional scanty mucoid sputum, were very distressing. On the night of August 29 he became worse and the following morning was admitted to hospital desperately ill, cold, shocked, and cyanosed, in a stuporous state feebly gasping for breath. The temperature was 100·4° F., pulse 110/min., respirations 45/min. Blood pressure was 95/70 mm. Hg. He died four hours later. An hour after death I performed bronchoscopy and saw the

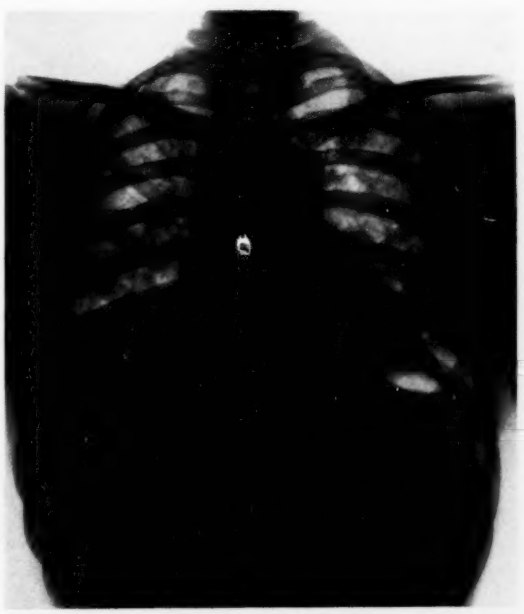


FIG. 1.—Chest radiograph in full inspiration taken on April 7, 1954. Appearances of pulmonary fibrosis: raised diaphragm (on screening respiratory excursion was greatly reduced), mediastinum drawn out, abnormal opacities most marked in the upper zones, trachea curved to the right side.

*Since submitting this report the man who replaced him at work has died of the same disease, and I have found two ambulant cases.

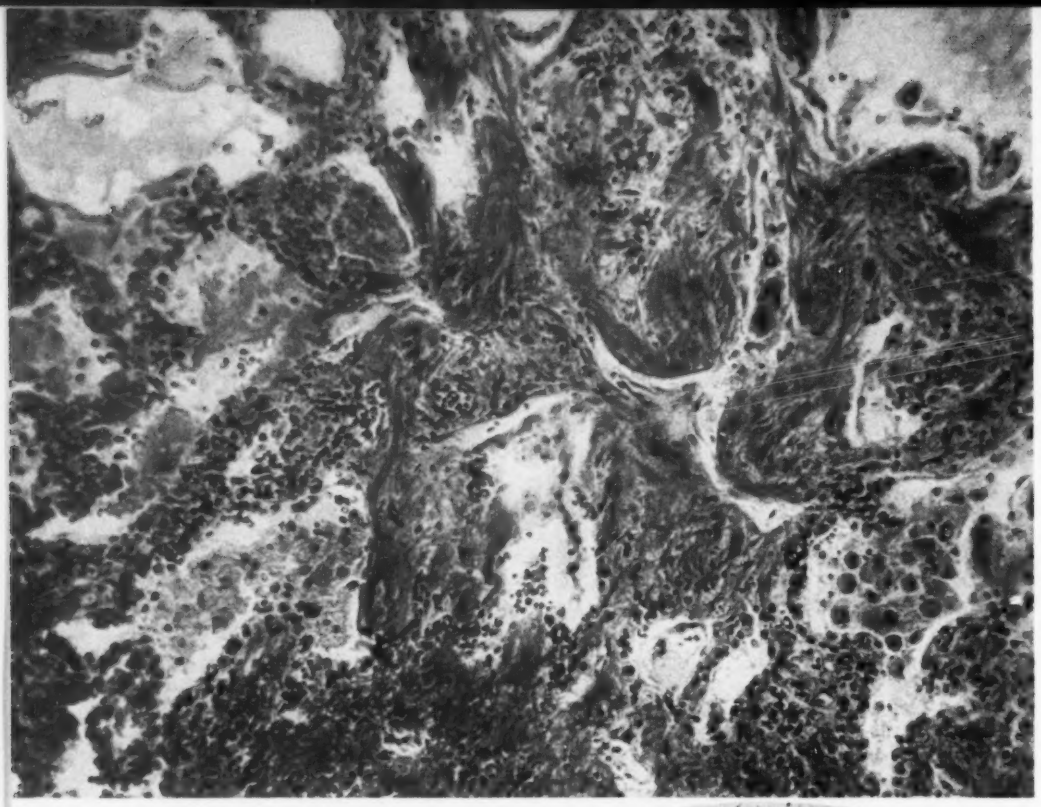


FIG. 2.—Section of lung showing fibrosis. (van Giesen) × 400.

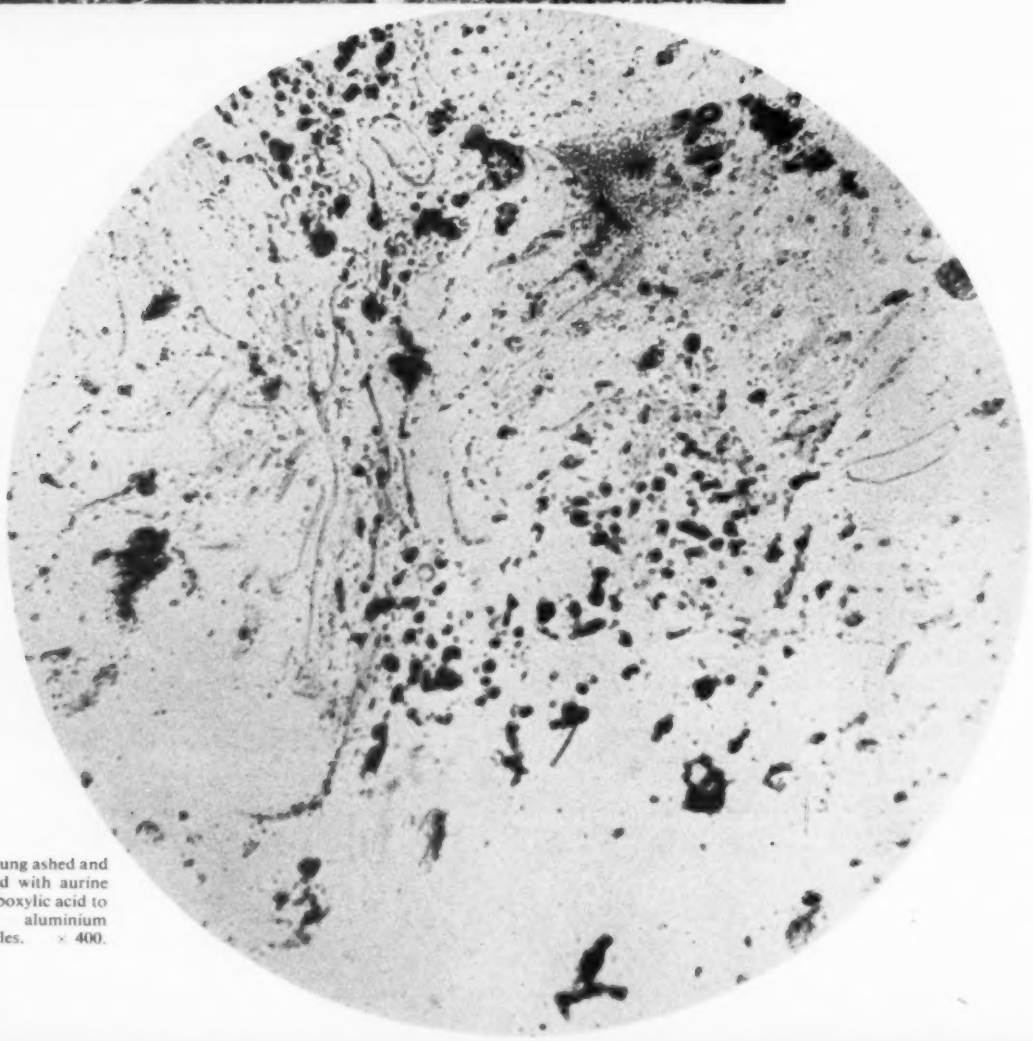


FIG. 3.—Lung ashed and stained with aurine tricarboxylic acid to show aluminium particles. × 400.

mucous membrane pale and glistening and normal throughout; no secretions were seen.

Five months before he died I admitted him to hospital for investigation and found a healthy-looking, slightly built young man. Respiratory excursion was poor, and medium crepitations were heard, mainly over the pectoral and sub-pectoral regions. The pulmonary second sound was considerably increased and palpable and there was a systolic thrust over the lower end of the sternum. The plain chest radiograph showed the appearances of pulmonary fibrosis (Fig. 1); the barium swallow looked normal. There was no albumin or sugar in the urine; the deposit looked normal under the microscope and there was no growth on culture. Nineteen specimens of sputum were examined for acid-fast bacilli, with negative results. There were no fungi found in the sputum. The total and differential white cell count was normal on two occasions and the erythrocyte sedimentation rate normal on three occasions. The plasma proteins were normal. The tuberculin test was negative to the 1/100 solution. The Wassermann and Kahn tests were negative. A patch test was carried out, applying the aluminium powder from the factory to his skin for 48 hours, with negative result. He was thought to be suffering from pulmonary fibrosis and cor pulmonale.

The possibility of aluminium fibrosis was considered and the nature of his work more fully investigated. He was engaged, with two other men, on an eight-hour shift rota to attend heavy stamping machines which produced finely divided aluminium powder. His work involved exposure to this dust in varying concentrations, over approximately half of his working day. The range of particle size of this powder is large but the quantity of dust in the atmosphere below 5μ is of the order of 10 mg. per c.m. In order to facilitate the process the dust is mixed with a small quantity of stearine which may form up to 0·5% of the total weight. This forms a fine film of aluminium stearate on the surface of the particle. It is of interest to note that during the second world war when cases of aluminium fibrosis occurred in Germany they were attributed to the absence of stearine due to war-time shortage. The two other men working on the plant, as well as several others doing similar work on a coarser type of powder, were examined and chest films of the other workers taken. None of them showed any evidence of lung fibrosis.

Pathology

Post-mortem examination showed all the organs, except the lungs and heart, to be normal to the naked eye and on microscopy. The lungs, which were prepared by the Gough technique, were lightly adherent to the chest wall. They were shrunken and on section showed marked generalized fibrosis and interstitial emphysema; the fibrosis was particularly marked in the upper lobes. The heart weighed 16 oz. (450 g.), the enlargement being mainly of the right ventricle. Microscopical examination of the lungs showed the fibrosis to be non-nodular (Fig. 2); numerous jagged particles were lying in the lung tissue (Fig. 3) and these gave histochemical reactions for aluminium. A frozen section showed some very small particles, which stained for lipoid, in the phagocytes in some of the alveoli; no other lipoid crystals or globules could be found. Chemical examination of the lung for aluminium gave the following results: root, 227 parts per million of wet lung estimated as aluminium; apex, 15 parts per million; base, a trace. The average content calculated on dry weight was 640 parts per million estimated as Al_2O_3.

Discussion

Pulmonary fibrosis of gradual onset in a previously fit young man, in whom tuberculosis, syphilis, sarcoidosis, malignant infiltration, lipoid pneumonia, the reticuloses, and the Hamman Rich syndrome can be excluded, is unique in my experience. The occupational disease reported by Shaver followed a clinical, radiological, and morbid anatomical and histological pattern that was characteristic. Wyatt and Riddell (1949) stated that the parenchymal fibrosis of the lungs was unlike anything previously encountered. The cases described by Goralewski followed a similar pattern. The patient described in this paper, except that he never had a spontaneous pneumothorax, bears a close resemblance clinically, radiologically, and pathologically to these cases. I suggest that the pulmonary fibrosis was due to a susceptible subject inhaling high concentrations of fine aluminium dust.

I gratefully acknowledge essential help from Dr. Peter Davies who showed the case to Dr. Shaver and his associates during his N.A.P.T. scholarship tour in Canada; from Dr. George Manning, who did the necropsy, histological and chemical examination, and from Professor R. E. Lane for the occupational history, particulars of dust exposure, and for his advice and encouragement.

References

Goralewski, G. (1947). *Z. ges. inn. Med.*, **2**, 665.
Hunter, D., Milton, R., Perry, K. M. A., and Thompson, D. R. (1944). *Brit. J. industr. Med.*, **1**, 159.
(1956). *Lancet*, **2**, 501 [leading article].
Perry, K. M. A. (1955). *Ibid.*, **2**, 463.
Shaver, C. G. (1948). *Occup. Med.*, **5**, 718.
Wyatt, J. P., and Riddell, A. C. R. (1949). *Amer. J. Path.*, **25**, 447.

Brit. J. industr. Med., 1959, **16**, 126.

TWO CASES OF HYDRAZINE HYDRATE DERMATITIS WITHOUT SYSTEMIC INTOXICATION

BY

DARRELL M. EVANS

From the United Kingdom Atomic Energy Authority

(RECEIVED FOR PUBLICATION SEPTEMBER 26, 1958)

Two patients exposed to hydrazine hydrate suffered contact dermatitis on the fingers of both hands, but remained free from systemic intoxication. The case histories are given, and a simple test is described for the detection of hydrazine both on the skin and in the atmosphere.

Hydrazine hydrate is an irritant which readily vaporizes. The irritant effects are not immediately noticeable. They develop gradually over several hours (Byrkit and Michalek, 1950). The local effects are inflammation of the skin and of the mucous membranes of the upper respiratory tract and eyes. Krop (1954) reports the occurrence of hydrazine dermatitis. Individual susceptibility to dermatitis varies. A specific sensitization may develop from short or long contact with many substances (Sequeira, Ingram, and Brain, 1947; Comstock, Lawson, Greene, and Oberst, 1954).

Systemic intoxication may follow absorption into the body by inhalation, by ingestion, or through the skin. Hydrazine is a liver poison, causing acute fatty degeneration and destruction of red blood cells (Sax, 1957; Comstock, *et al.*, 1954). The latter effect is disputed by some authors, but phenylhydrazine causes haemolysis of mature red blood cells and is used for treating cases of polycythaemia vera. A slight haemorrhagic pulmonary oedema may develop. The earliest symptoms in man may be anorexia and loss of weight, thus acting as a warning sign of an impending health hazard (Comstock *et al.*, 1954). No permanent ill effects are known to have occurred after recovery from a severe attack of poisoning.

The maximum allowable concentration of hydrazine hydrate is tentatively stated by the American Conference of Governmental Industrial Hygienists to be 1 p.p.m. in air (Sax, 1957).

Properties

Aqueous solutions of hydrazine are basic and act as a reducing agent. Hydrazine can be employed to reduce compounds of metals such as silver, gold, and copper to the metallic state. It is oxidized slowly in air at room temperatures (about 0·01% per hour), and reacts very readily with oxidizing compounds such as hydrogen peroxide, chlorates, and nitric acid. If hydrazine is allowed to come into contact with oxidizing acids it may decompose with explosive violence. Storage in an inert atmosphere reduces the tendency to oxidation, a fact which is particularly important to remember in quantitative analytical work. It decomposes catalytically in the presence of some active metals and oxides. As hydrazine attacks cork, rubber, and certain organic substances, contact with these must be avoided during storage. It can be stored in glass or polythene containers.

Industrial Uses

Hydrazine is used in the following processes (Audrieth, Mohr, and Mohr, 1951; Audrieth and Ogg, 1951):—Manufacture of certain drugs, such as isonicotinic acid and dye intermediates, and of certain plastic and rubber products; in rocket fuel; in photography; in the manufacture of certain insecticides, fungicides, and preservatives; in certain flux compositions in order to clean the metal and prevent further oxidation of the metallic surface; in boiler feed water to prevent corrosion as it removes dissolved oxygen; in the silvering of mirrors and plastics; as an agent for treating textiles, *e.g.*, uncrushable cloth; maleic hydrazide is used to retard plant growth.

Case Histories

Case 1 reported the day after he had used hydrazine hydrate when an irritating rash had developed. The distribution was on the dorsum and between the fingers of both hands. At this stage the palmar aspect was

unaffected. The rash consisted mainly of small vesicles, some of which had ruptured and small crusts had developed. There were fissures on two fingers. He stated that this was the fourth time he had developed dermatitis after using hydrazine hydrate. He was given an antipruritic lotion ("surfathesin"). He went away on holiday and was next seen 10 days later, when he had an exfoliative dermatitis with multiple fissures on the fingers of both hands. He was then treated with an antipruritic ointment ("eurax") and the condition improved. Unfortunately, soon after the dermatitis had healed he unwittingly came into contact with hydrazine hydrate again. Within seven hours his fingers were irritating and next morning he had developed a recurrence of the rash on his fingers.

Case 2 was seen two or three weeks after the onset of the rash, when several blisters were seen on the fingers. There had been a history of using hydrazine hydrate just before developing the rash. He had had a similar condition previously, also after contact with hydrazine hydrate.

Neither of the cases mentioned showed any signs of systemic intoxication. They had both been in contact with hydrazine hydrate at irregular intervals for about five months before developing a rash for the first time.

Rapid Test for Detecting Hydrazine

An aqueous solution of hydrazine reacts with 1·5% alcoholic solution of picryl chloride in neutral or mildly alkaline solution to form a pink violet colour. The test is reported to be effective in concentrations down to 1:400,000 (Kalberg and Cherkesov, 1951; *Chemical Abstracts*, 1952).

This test was modified in order to detect the presence of hydrazine on the fingers. A filter paper was impregnated with 1·5% alcoholic solution of picryl chloride and the fingers were pressed onto the paper, which was then held in the vapour over an unstoppered bottle of ammonia. The places which had been in contact with the skin changed from yellow to blue, sometimes being encircled by a red ring, if hydrazine was present.

This test was positive in Cases 1 and 2 and in another man who had worked with hydrazine hydrate but did not develop dermatitis. The latter man and Case 1 still showed a positive result to this skin test one day after contact in spite of normal washing. It seems likely that the reasons for hydrazine persisting on the fingers are, first, that there are no readily reducible substances in the epidermis, and secondly, being a basic substance, hydrazine penetrates the epidermal cells and is not readily washed off.

Hydrazine vapour can be detected in the air by placing test papers of picryl chloride at suitable points in the laboratory. A colour change occurs as described above. For greater sensitivity to low concentrations of hydrazine vapour a standardized gas flow absorption method using the same reagent can be used.

Precautions in Handling Hydrazine

These observations confirm the need to keep hydrazine confined so far as is possible, and when it is being used there should be adequate ventilation. Gloves and goggles may be required for repeated handling. Lanoline should be used to protect the exposed skin surfaces. Eye wash bottles filled with fresh water should be readily at hand.

When dealing with large quantities of hydrazine breathing apparatus is required and a bath of fresh tepid water should be readily available for rapid decontamination of the skin.

I wish to thank the United Kingdom Atomic Energy Authority for permission to publish this paper. I would also like to thank Messrs. K. T. B. Scott and S. W. Maxted for their advice on the chemistry of hydrazine.

References

Audrieth, L. F., and Ogg, B. A. (1951). *Chemistry of Hydrazine*. Chapman & Hall, London.

——, Mohr, P. H., and Mohr, E. B. (1951). In *Encyclopedia of Chemical Technology*, ed. R. E. Kirk and D. F. Othmer, Vol. 7, p. 575. Interscience Encyclopedia, Inc., New York.

Byrkit, G. D., and Michalek, G. A. (1950). *Industr. Engng Chem.*, **42**, 1862.

Chemical Abstracts (1952), **46**, 2960 C.

Comstock, C. C., Lawson, L. H., Greene, E. A., and Oberst, F. W. (1954). *A.M.A. Arch. industr. Hyg.*, **10**, 476.

Kalberg and Cherkesov (1951). *Zhur. anal. Khim.*, **6**, 347.

Krop, S. (1954). *A.M.A. Arch. industr. Hyg.*, **9**, 199.

Sax, N. I. (1957. *Dangerous Properties of Industrial Materials*, p. 761. Reinhold, New York.

Sequeira, J. H., Ingram, J. T., and Brain, R. T. (1947). *Diseases of the Skin*, 5th ed., p. 350. Churchill, London.

Brit. J. industr. Med., 1959, **16**, 128.

THE CHEMOTHERAPY OF POISONING BY ORGANOPHOSPHATE ANTICHOLINESTERASES

BY

D. R. DAVIES and A. L. GREEN

From the Chemical Defence Experimental Establishment, Porton, Wilts.

(RECEIVED FOR PUBLICATION OCTOBER 10, 1958)

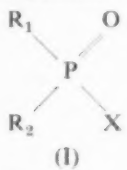
Oximes (with or without atropine as an adjunct) have recently been used successfully in the treatment of humans poisoned by organophosphate anticholinesterases. The discovery of the nature of the biochemical lesion in organophosphate poisoning has permitted the design of drugs to repair specifically this particular lesion. This paper reviews historically the researches which led to the development of pyridine-2-aldoxime methiodide (PAM) and its corresponding methanesulphonate (P2S), the two most successful oximes yet tried, and summarizes the theoretical background to their rational use.

Organophosphates are lethal because they inactivate cholinesterase due to phosphorylation of the enzyme's active centre. Consequently two rational lines of treatment are: (*a*) To find some compound which could be phosphorylated as rapidly as the enzyme and which, if introduced into the body, would protect the enzyme from inhibition by competing with it for the organophosphate, or (*b*) to find a compound which would restore the activity of the inhibited enzyme by dephosphorylating it. In both cases essentially the same type of compound is needed, namely, one with a high intrinsic reactivity with organophosphoryl compounds, in (*a*) with the inhibitor itself or in (*b*) with the phosphorylated enzyme. Types of compounds with either or both of these properties are *o*-dihydroxybenzene derivatives, metal chelates, hydroxylamine, hydroxamic acids, and oximes. Pyridine-2-aldoxime methiodide and methanesulphonate have been by far the most successful as reactivators and in the treatment of poisoned animals.

A brief account is given of the range of compounds for which PAM has been shown to be a successful antidote in intact animals and of the ability of PAM to overcome the signs and symptoms of poisoning both in animals and in man.

Possible lines of future investigations are indicated.

Organophosphates with the general structure (I) are among the most toxic of all simple chemical compounds.



(I)

R_1 and R_2 are alkyl, alkoxy, or alkylamino groups and X is an acid radical such as fluoride, *p*-nitrophenoxy, or dialkylphosphate.

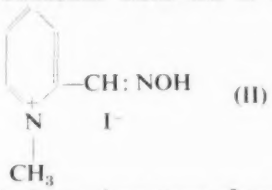
The signs and symptoms of poisoning include muscarinic, nicotinic, and central nervous system effects, all of which can be attributed to the accumulation of endogenously produced acetylcholine (Koelle and Gilman, 1949). Muscarinic effects include nausea, pallor, sweating, salivation, abdominal cramps, vomiting, involuntary defaecation and urination, miosis, excessive bronchial secretion, and bronchoconstriction. Nicotinic effects include muscular fasciculations and weakness, and in severe poisoning muscular paralysis. Effects in the central nervous system include giddiness, headache, unconsciousness, and finally paralysis of the respiratory centre (Grob, 1956). Death in animals is almost invariably due to respiratory failure resulting from paralysis of the respiratory muscles or respiratory centre, from bronchoconstriction, or from a combination of these effects (de Candole, Douglas, Evans, Holmes, Spencer, Torrance, and Wilson, 1953).

Organophosphates are widely used as insecticides, have some use in medicine in the treatment of myasthenia and glaucoma, and have been considered as potential chemical warfare agents. Fortunately,

these compounds have not been used in war, but their incautious use in agriculture and their deliberate use as suicidal agents have confronted the physician with an urgent need for satisfactory antidotes.

The early recognition of the similar clinical picture in poisoning by organophosphates and by eserine soon led to the realization that these newer compounds were, like eserine, highly potent anticholinesterases (Adrian, Feldberg, and Kilby, 1947), and that poisoning could be countered by antagonists to the action of acetylcholine, notably atropine. For many years atropine has remained the sole practical antidote to organophosphate poisoning, supported by artificial respiration when needed (Grob, 1956). Unfortunately atropine has many deficiencies. It has highly undesirable physiological effects in its own right and furthermore it will only counteract the muscarinic and some of the central effects of acetylcholine and not the nicotinic effects. Attempts to incorporate acetylcholine antagonists active at neuromuscular junctions in therapeutic mixtures with atropine have sometimes been successful in animals (Parkes and Sacra, 1954) but have not led to any recommended treatment in humans.

In the last three years a group of new drugs, of which the best known is PAM (pyridine-2-aldoxime methiodide or 2-hydroxyiminomethyl-N-methyl pyridinium iodide) (II), has been introduced, which will reverse neuromuscular block due to organophosphates and, in less serious cases of poisoning, may obviate the need for atropine as well. These drugs are not acetylcholine antagonists but work on a completely different principle. Since they are likely to be used in future cases of accidental poisoning it has been thought worth while to give a brief account of their history, of how they act, and of their potentialities in medicine.



(II)

Rationale and Development of Newer Antidotes

When the anticholinesterase action of organophosphates was studied kinetically *in vitro*, it was found that inhibition was progressive with time and, in contrast to inhibition with eserine, was effectively irreversible by dilution or dialysis (Mackworth and Webb, 1948). Further experiments showed that during inhibition the organophosphate combined directly and rapidly with some part of the active centre of the enzyme, resulting in the enzyme being

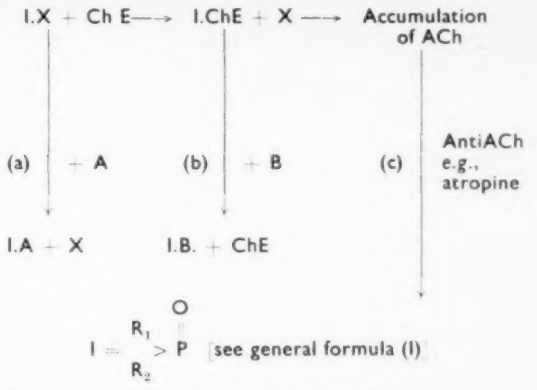
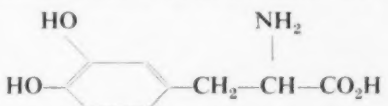


FIG. 1—Diagrammatic scheme of poisoning by organophosphate anticholinesterases.

phosphorylated (Wilson, 1954; Aldridge, 1954). This suggested the possibility of more fundamental methods of treating organophosphate poisoning. The mechanism of inhibition and the various ways of treatment are illustrated in Fig. 1. The first possible method (*a*), essentially prophylactic,* is to find some compound (A) which could be phosphorylated as rapidly as the enzyme and which, if introduced into the body, would protect the enzyme from inhibition by competing with it for the organophosphate. The second method (*b*) is to find some compound (B) which would restore the activity of the inhibited enzyme by dephosphorylating it. In both cases essentially the same type of compound is needed, namely, one with a high intrinsic reactivity with organophosphoryl compounds, in (*a*) with the inhibitor itself, or in (*b*) with the phosphorylated enzyme. Accordingly the search for such compounds has generally proceeded along much the same lines.

As a starting point the fact that organophosphates reacted very rapidly with enzymic proteins suggested that their reactivity with simple amino-acids should be examined. Of the normal amino-acids in proteins only tyrosine (Ashbolt and Rydon, 1952) and histidine (Wagner-Jauregg and Hackley, 1953) showed any reactivity at all and even this was not great, but one of the rarer amino-acids, dihydroxyphenylalanine (DOPA) (III), did combine surprisingly quickly with some of the more reactive organophosphates such as sarin, DFP, and



(III)

*In this article prophylaxis is defined as treatment before poisoning and therapy as treatment after poisoning.

tabun* (Jandorf, Wagner-Jauregg, O'Neill, and Stolberg, 1952; Augustinsson, 1952; Berry, Fellowes, Fraser, Rutland, and Todrick, 1955). This reactivity was in fact independent of the amino-acid portion of the molecule and was entirely due to the *o*-dihydroxyphenyl side-chain. A number of *o*-dihydroxybenzene derivatives were subsequently tested, but the reactivities of all of them fell in a fairly narrow range and for any individual compound the reactivity could be predicted reasonably well from the ionization constant (Epstein, Rosenblatt, and Demek, 1956). No evidence has been given that any of these compounds reactivate inhibited cholinesterase or possess any antidotal activity.

Another approach to compounds capable of decomposing organophosphates is based upon the catalytic effect of heavy metal ions on hydrolytic reactions. Metal ions, particularly when kept from precipitation in neutral solution by amine-complexing agents, for example, by 2:2′—dipyridyl (IV), proved to be very effective catalysts for the

(IV)

hydrolysis of organophosphates (Wagner-Jauregg, Hackley, Lies, Owens, and Proper, 1955; Courtney, Gustafson, Westerback, Hyytiainen, Chaberek, and Martell, 1957), while ammonium molybdate is a potent reactivator of inhibited cholinesterase (Hobbiger, 1956) but none of these metal derivatives have yet been shown to have any value in treatment.

The third source of reactants with organophosphates has proved easily the most profitable. Hydroxylamine (V) reacts almost instantaneously with carboxylic esters, and in the hope that the same

NH_2OH (V)

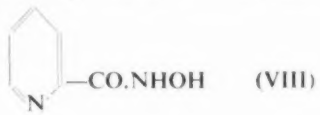
thing would happen with phosphate esters, the reaction of hydroxylamine with sarin was studied (Jandorf, 1956).† The sarin was decomposed, but relatively slowly. In an attempt to improve on this reactivity many substituted hydroxylamines were examined, eventually leading to the discovery of the high reactivity with organophosphates of hydroxamic acids (Hackley, Plapinger, Stolberg, and Wagner-Jauregg, 1955) and oximes (Green and Saville, 1956). Before the publication of this work hydroxylamine had been tested independently as a possible reactivator of inhibited cholinesterase (Wilson, 1952). Some success was achieved with this reagent and also with choline (VI). Choline's reactivating properties were attributed to its ability

$(CH_3)_3N^+CH_2CH_2OH$ (VI)

to attach itself to the inhibited enzyme by electrostatic attraction between its quaternary ammonium group and the so-called "anionic site" on the inhibited enzyme. The "anionic site" is the name given to that part of cholinesterase to which the choline part of acetylcholine becomes anchored during normal hydrolysis. To try to combine in one compound the active chemical groups of hydroxylamine and choline, namely the hydroxyamino group and the quaternary ammonium group, nicotinhydroxamic acid methiodide (VII) was synthesized (Wilson and Meislich, 1953). This

(VII)

compound proved a better reactivator than either hydroxylamine or choline, although it was shown that other hydroxamic acids were better still, particularly picolinhydroxamic acid (VIII) which does not possess a quaternary ammonium group (Wilson and Ginsburg, 1955a; Jandorf, Crowell,



(VIII)

and Levin, 1955). Even so, the activity was still of a comparatively low order. A number of hydroxamic acids have been tested as antidotes to poisoning by sarin (Askew, 1956; Epstein and Freeman, 1956) and by DFP (Funke, Benoit, and Jacob, 1955) but they were only effective in doses far too high to be of practical significance. Studies of the effect of structure on the direct reactivity of hydroxamic acids with organophosphates showed that the deciding factor was, as with the dihydroxybenzenes, the ionization constant and that the reactivity could be predicted reasonably accurately from the ionization constant alone (Stolberg and Mosher, 1957; Green, Sainsbury, Saville, and Stansfield, 1958). It was also possible to show that for reactivity at physiological *p*H (7·4), there was an optimum ionization constant equivalent to a pK_a of about 8 (Steinberg, Swidler, and Seltzer, 1957). To test this principle in reactivation many hydroxylamine derivatives were synthesized with pK_as ranging

*The formulae of all the organophosphates referred to will be found in Table I.

† This work was originally published as a classified report in 1951.

from 5 to 12 (Childs, Davies, Green, and Rutland, 1955). Most of them did reactivate *in vitro* and the best compounds at *p*H 7·4 have a pK_a around 8, but this factor alone was not decisive. With some exceptions, oximes with this *p*K tended to be more active than analogous hydroxamic acids. In particular, the oxime PAM (II) was far more active than any other compound tested (Davies and Green, 1955). Meanwhile following the idea that quaternary ammonium groups were important in reactivation, PAM had been synthesized independently and its effectiveness *in vitro* confirmed (Wilson and Ginsburg, 1955b). This effectiveness is almost certainly due to the presence in PAM of a nucleophilic oxime group and a quaternized nitrogen atom situated at such a distance from the oxime group that it can interact strongly with the "anionic site" on the inhibited enzyme (Green and Smith, 1958).

Treatment of Poisoned Animals with Oximes

Many oximes have been tested as antidotes to organophosphates with considerable success. In conjunction with atropine PAM was effective against almost all the more common organophosphate anticholinesterases, although when given alone its activity was generally small. In sarin-poisoned rats 1:2-dione monoximes were far more active than PAM when given without atropine (Askew, 1956; Dultz, Epstein, Freeman, Gray, and Weil, 1957). Since there was a possibility that with these compounds atropine could be dispensed with altogether, they were explored in some detail, but the early promise was not maintained. In species other than rats and against organophosphates other than sarin, their effectiveness was much less and was in general not enhanced by atropine to anything like the same extent as was the effectiveness of PAM (Askew, 1957). A further disadvantage was that the more generally applicable of these compounds, namely 2-oxo-aldoximes such as isonitrosoacetone (MINA) (IX) were moderately toxic being converted *in vivo* to cyanide (Askew, Davies, Green, and Holmes, 1956). The high therapeutic activity of

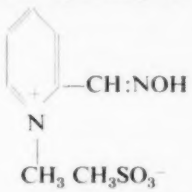
$$CH_3.CO.CH{:}NOH \qquad (IX)$$

1:2-dione-monoketoximes, such as diacetylmonoxime (DAM) (X), in sarin-poisoned rats

$$CH_3.CO.C(CH_3){:}NOH \qquad (X)$$

remains an anomaly, as their *in vitro* reactivating powers are relatively low, while their intrinsic reactivity with sarin is considerably less than that of hydroxamic acids (Askew, Davies, and Green, 1957).

Since the discovery of PAM, its therapeutic value in animals has been widely demonstrated. Table 1 summarizes the results obtained by various authors in the treatment by PAM (or P2S the methanesulphonate salt corresponding to PAM, XI) plus



(XI)

atropine of poisoning by organophosphate anticholinesterases of most of the types likely to be met in practice. The assessment in the "effect" column is necessarily only crudely quantitative as different authors have generally used different doses of PAM, have adopted different routes of administration, and have given treatment at varied times relative to poisoning. All the compounds which give a form of phosphorylated cholinesterase readily susceptible to reactivation *in vitro* by PAM have been successfully treated. These compounds are all of structure (I) in which R_1 and R_2 are alkyl or alkoxy groups, but not alkylamino groups. Since in the phosphorylated enzyme the group X is not present, its nature is immaterial. However, phosphorylated cholinesterases (particularly those containing two methoxy or isopropoxy groups) although initially reactivatable become impossible to reactivate after storage both *in vitro* (Jandorf, Michel, Schaffer, Egan, and Summerson, 1955; Wilson, 1955; Davies and Green, 1956) and *in vivo* (Hobbiger, 1956; Vandekar and Heath, 1957). With the inhibited enzyme in this form there is at present no known method of reactivation (Aldridge, 1956).

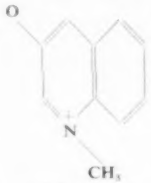
Treatment of parathion poisoning presents a rather different problem from treatment of poisoning by most other organophosphates. Parathion is converted *in vivo* to paraoxon which is the true lethal agent. As this conversion is slow, repeated dosing with PAM may be necessary before treatment is completely successful (Wilson and Sondheimer, 1957).

In a general sense the antidotal activity of PAM is almost certainly due to its reactivating powers. Animals poisoned with eserine, which does not give a phosphorylated enzyme, or with tabun or OMPA, which give amidophosphoryl enzymes relatively resistant to reactivation, could not be satisfactorily treated with PAM (Kewitz, Wilson, and Nachmansohn, 1956; Bethe, Erdmann, Lendle, and Schmidt, 1957; Wilson and Sondheimer, 1957).

In spite of this, several problems arise when the antidotal action of PAM in intact animals is considered in detail. Most investigations on treatment with PAM have been mainly concerned with survival

TABLE 1

EFFECT OF PAM (OR P2S) PLUS ATROPINE ON ORGANOPHOSPHATE POISONING IN ANIMALS

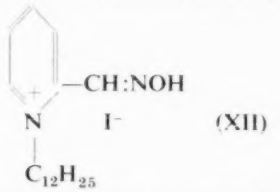
Toxic Agent				Species	Effect	Reference*
Code Name	Formula					
	R_1	R_2	X			
Demeton methyl	MeO	MeO	$SC_2H_4S.Et$	Mice	+ +	e
				Rabbits	+ +	e
TEPP	EtO	EtO	$(EtO)_2\ PO_2$	Mice	+ + +	d f j
				Rats	+ + +	d
				Guinea-pigs	+ + +	d
				Rabbits	+ + +	d
Paraoxon	EtO	EtO	$O.C_6H_4NO_2$	Mice	− − +	f g
				Guinea-pigs	+ + +	b
Parathion	EtO	EtO	$O.C_6H_4NO_2$	Mice	− −	e j
			(P = S not P = O)	Guinea-pigs	+ +	b
				Dogs	+ +	h
Ro. 3-0422	EtO	EtO		Mice	+ + +	f
Ro. 3-0340	EtO	EtO	$O.C_6H_4N\ Me_2^+$	Mice	+ + +	
Ro. 3-0351	*i*PrO	*i*PrO		Mice	+ + +	
DFP	*i*PrO	*i*PrO	F	Mice	+ +	f g
				Guinea-pigs	+ +	b
Sarin	*i*PrO	Me	F	Mice	+ +	a d j
				Rats	+ +	a d
				Guinea-pigs	+ + +	a d
				Rabbits	+ + +	d i
				Dogs	+ + +	i
Tabun	Me_2N	EtO	CN	Mice	+	j
				Dogs	+	c
OMPA	Me_2N	Me_2N	$(Me_2N)_2\ PO_2$	Mice	—	g

*REFERENCES

a. Askew (1957)
b. Bethe *et al.* (1957)
c. Brown *et al.* (1957)
d. Davies *et al.* (1959)
e. Fournel (1958)
f. Hobbiger (1957)
g. Kewitz *et al.* (1956)
h. Pepu and Bianchi (1958)
i. Wills *et al.* (1957)
j. Wilson and Sondheimer (1957)

and there is surprisingly little information on how far PAM will counteract the clinical effects of poisoning in animals from non-lethal doses of organophosphate. However, PAM does not generally seem to counteract muscarinic signs, such as salivation and sweating (Hobbiger, 1957), although it will overcome miosis (Kewitz *et al.*, 1956), nor, in the absence of atropine, does it seem to have much effect on central depression of respiration (Brown, Kunkel, Somers, and Wills, 1957). With atropine, it has very marked and beneficial actions upon respiratory failure, which appear to be primarily due to the reversal of neuromuscular block in the respiratory muscles (Brown *et al.*, 1957; Wills, Kunkel, Brown, and Groblewski, 1957). The ability of PAM to overcome neuromuscular block had previously been shown on isolated tissue preparations (Holmes and Robins, 1955). It will also counteract the bradycardia due to organophosphates and this too may contribute to its therapeutic activity (Bethe *et al.*, 1957). The inability to overcome central respiratory depression may be due to failure of PAM, a quaternary salt, to penetrate into the central nervous system. In intact poisoned animals PAM will rapidly restore blood and muscle cholinesterase but very little effect has been observed on inhibited brain cholinesterase (Hobbiger, 1957; Rutland, 1957; Kewitz, 1957; Kewitz and Nachmansohn, 1957). The relative inability of PAM to enter rat brain has been confirmed by direct estimation of tissue concentrations (Creasey, unpublished results). An attempt to overcome this deficiency was made by

synthesis of a modification of PAM, termed PAD (XII), which still possessed reactivating properties but which was fat-soluble (Wilson, 1958). Although



(XII)

this compound did enhance the effect of PAM plus atropine in sarin-poisoned mice, the overall effect was less than that reported by other authors using PAM plus atropine alone (Askew, 1957; Davies, Green, and Willey, 1959) so that the significance of PAD remains uncertain. Its almost complete lack of water solubility makes it of doubtful medicinal value.

Treatment of Organophosphate Poisoning in Man

The promising results with animals have encouraged the cautious use of PAM in man. In Japan where accidental poisoning with parathion has become a serious problem, PAM has been tried with considerable success (Namba and Hiraki, 1958). Treatment in 39 cases of human poisoning has been described (Namba, 1958), of which 27 exhibited moderate to severe symptoms. In most cases PAM was given without atropine. In all but five of the more severe cases, signs of parathion poisoning almost completely disappeared after the intravenous injection of about 1 g. of PAM. In the other cases further improvement was generally obtained by giving additional PAM. Only one patient died despite being given 2 g. of PAM together with 2 mg. of atropine. This patient had taken a very large amount of parathion with the intention of committing suicide. The most striking effects on the course of poisoning were the disappearance of the signs of neuromuscular block, fasciculations and muscle cramps (which cannot be countered by atropine), and also the complete disappearance of disturbances of consciousness. Some of the muscarinic signs such as salivation and excessive bronchial secretion were also dispersed.

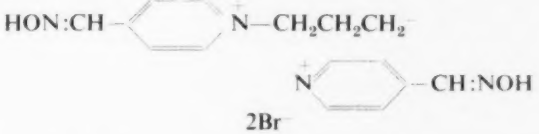
The remarkable effect of PAM in clearing consciousness was also noted in a case of suicidal parathion poisoning in Denmark (Karlog, Nimb, and Poulsen, 1958). This effect is difficult to explain if the blood-brain barrier in man is as resistant to the penetration of PAM as it appears to be in animals.

The ability of PAM to counteract the nicotinic signs of anticholinesterase poisoning in man has been confirmed (Grob and Johns, 1958) but no corresponding effect was found on muscarinic or central nervous system signs. The discrepancy between these results and those with parathion described above remains unexplained. There is, however, some evidence that after poisoning with the same anticholinesterase all species do not react equally well to a given reversing agent. It is, therefore, not possible to predict accurately how man would respond to PAM treatment solely on the basis of observations on animals.

Pyridine-2-aldoxime methiodide (and its corresponding methane sulphonate, P2S) is relatively harmless to animals in therapeutically active doses, and it has been suggested from animal experiments that at least 30 mg./kg. could be given intramuscularly to man with impunity (Davies and Willey, 1958). In normal human subjects P2S has been given without ill-effects in doses of over 5 g. orally or, as a 15% aqueous solution, in doses of over 1 g. intramuscularly (Ladell, 1958). For intramuscular injection P2S is preferable to PAM because of its vastly increased water solubility. Pyridine-2-aldoxime methiodide itself has been administered intravenously to man quite safely in doses of up to 2g. (Namba and Hiraki, 1958; Grob and Johns, 1958).

Possible Future Progress

Although PAM and P2S have proved successful in both animals and man the development of even better drugs by applying the same principles is still possible. Thus, a new series of compounds has been described recently (Poziomek, Hackley, and Steinberg, 1958) which will reactivate inhibited cholinesterase even more quickly than will PAM and which may be more effective still as therapeutic agents. These compounds are obtained by the coupling of two hydroxyiminomethylpyridine molecules of PAM linked together, e.g., compound TMB4 (XIII). These results have been confirmed (Berry, Davies, and Green, 1959; Hobbiger,



(XIII)

O'Sullivan and Sadler, 1958), but it has been shown that the increased reactivating power is retained by related compounds with only one oxime group and is almost certainly due to the presence of the second charged nitrogen atom.

A source of future antidotes which has not been completely investigated is the metal complexes

referred to previously. These complexes are still the most effective reagents known for decomposing organophosphate anticholinesterases, yet very few of them appear to have been tested *in vivo*.

Beside the possible discovery of still better reactants or reactivators, treatment with PAM or P2S may be made more effective by the use of adjuncts other than atropine, given either in addition to atropine or in place of atropine. The fact that no more effective substitute than atropine has been found when given alone does not imply that atropine is necessarily the best adjunct to oximes.

In presenting this review, we have attempted to show how the elucidation of the biochemical lesion in organophosphate poisoning has led fairly quickly to improved therapeutic measures of considerable practical value. While in other cases of poisoning the same methods may be slower in producing a satisfactory form of treatment, nevertheless this procedure does offer a better chance of finding such treatment than the more usual symptomatic approach. Its success against organophosphate poisoning does much to justify the expenditure of considerable effort upon understanding fundamental mechanisms of toxicity.

References

Adrian, E. D., Feldberg, W., and Kilby, B. A. (1947). *Brit. J. Pharmacol.*, **2**, 56.

Aldridge, W. N. (1954). *Chem. and Ind.*, p. 473.

—— (1956). *A. R. chem. Soc.*, **53**, 294.

Ashbolt, R. F., and Rydon, H. N. (1952). *J. Amer. chem. Soc.*, **74**, 1865.

Askew, B. M. (1956). *Brit. J. Pharmacol.*, **11**, 417.

—— (1957). *Ibid.*, **12**, 340.

——, Davies, D. R., and Green, A. L. (1957). *Biochem. J.*, **66**, 43P.

——, ——, ——, and Holmes, R. (1956). *Brit. J. Pharmacol.*, **11**, 424.

Augustinsson, K. B. (1952). *Acta chem. scand.*, **6**, 959.

Berry, W. K., Davies, D. R., and Green, A. L. (1959). *Biochem. J.*, **71**, 15P.

——, Fellowes, K. P., Fraser, P. J., Rutland, J. P., and Todrick, A. (1955). *Ibid.*, **59**, 1.

Bethe, K., Erdmann, W. D., Lendle, L., and Schmidt, G. (1957). *Naunyn-Schmiedeberg's Arch. exp. Path. Pharmakol.*, **231**, 3.

Brown, R. V., Kunkel, A. M., Somers, L. M., and Willis, J. H. (1957). *J. Pharmacol. exp. Ther.*, **120**, 276.

Candole, C. A. de, Douglas, W. W., Evans, C. L., Holmes, R., Spencer, K. E. V., Torrance, R. W., and Wilson, K. M. (1953). *Brit. J. Pharmacol.*, **8**, 466.

Childs, A. F., Davies, D. R., Green, A. L., and Rutland, J. P. (1955). *Ibid.*, **10**, 462.

Courtney, R. C., Gustafson, R. L., Westerback, S. J., Hyytiainen, H., Chaberek, S. C., and Martell, A. E. (1957). *J. Amer. chem. Soc.*, **79**, 3030.

Davies, D. R., and Green, A. L. (1955). *Disc. Faraday Soc.*, **20**, 269.

——, —— (1956). *Biochem. J.*, **63**, 529.

Davis, D. R., and Willey, G. L. (1959). *Brit. J. Pharmacol.* Vol. 14 (March issue still in press).

——, and Willey, G. L. (1958). *Ibid.*, **13**, 202.

Dultz, L., Epstein, M. A., Freeman, G., Gray, E. H., and Weil, W. B. (1957). *J. Pharmacol. exp. Ther.*, **119**, 522.

Epstein, J., Rosenblatt, D. H., and Demek, M. M. (1956). *J. Amer. chem. Soc.*, **78**, 341.

Epstein, M. A., and Freeman, G. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **92**, 660.

Fournel, J. (1958). *C. R. Soc. Biol. (Paris)*, 1957, **151**, 1373.

Funke, A., Benoit, G. and Jacob, J. (1955). *C. R. Acad. Sci. (Paris)*, **240**, 2575.

Green, A. L., Sainsbury, G. L., Saville, B., and Stansfield, M. (1958). *J. chem. Soc.*, p. 1583.

——, and Saville, B. (1956). *Ibid.*, p. 3887.

——, and Smith, H. J. (1958). *Biochem. J.*, **68**, 32.

Grob, D. (1956). *A.M.A. Arch. intern. Med.*, **98**, 221.

——, and Johns, R. J. (1958). *J. Amer. med. Ass.*, **166**, 1855.

Hackley, B. E., Plapinger, R., Stolberg, M., and Wagner-Jauregg, T. (1955). *J. Amer. Chem. Soc.*, **77**, 3651.

Hobbiger, F. (1956). *Brit. J. Pharmacol.*, **11**, 295.

—— (1957). *Ibid.*, **12**, 438.

——, O'Sullivan, D. C., and Sadler, P. W. (1958). *Nature, Lond.*, **182**, 1498.

Holmes, R., and Robins, E. L. (1955). *Brit. J. Pharmacol.*, **10**, 490.

Jandorf, B. J. (1956). *J. Amer. Chem. Soc.*, **78**, 3686.

——, Crowell, E. A., and Levin, A. P. (1955). *Fed. Proc.*, **14**, 231.

——, Michel, H. O., Schaffer, N. K., Egan, R., and Summerson, W. H. (1955). *Disc. Farad. Soc.*, **20**, 134.

——, Wagner-Jauregg, T., O'Neill, J. J., and Stolberg, M. A. (1952). *J. Amer. chem. Soc.*, **74**, 1521.

Karlog, O., Nimb, M., and Poulsen, E. (1958). *Ugeskr. Laeg.*, **120**, 177.

Kewitz, H. (1957). *Arch. Biochem.*, **66**, 263.

——, and Nachmansohn, D. (1957). *Ibid.*, **66**, 271.

——, Wilson, I. B., and Nachmansohn, D. (1956). *Ibid.*, **64**, 456.

Koelle, G. B., and Gilman, A. (1949). *Pharmacol. Rev.*, **1**, 166.

Ladell, W. S. S. (1958). *Brit. med. J.*, **2**, 141.

Mackworth, J. F., and Webb, E. C. (1948). *Biochem. J.*, **42**, 91.

Namba, T. (1958). *Naika no Ryoiki* (Field of Internal Medicine), **6**, 84.

——, and Hiraki, K. (1958). *J. Amer. med. Ass.*, **166**, 1834.

Parkes, M. W., and Sacra, P. (1954). *Brit. J. Pharmacol.*, **9**, 299.

Pepeu, G., and Bianchi, C. (1958). *Boll. Soc. ital. Biol. sper.*, **34**, 444.

Poziomek, E. J., Hackley, B. E., and Steinberg, G. M. (1958). *J. org. Chem.*, **23**, 714.

Rutland, J. P. (1957). *Biochem. J.*, **66**, 43P.

Steinberg, G. M., Swidler, R., and Seltzer, S. (1957). *Science*, **125**, 336.

Stolberg, M. A., and Mosher, W. A. (1957). *J. Amer. chem. Soc.*, **79**, 2618.

Vandekar, M., and Heath, D. F. (1957). *Biochem. J.*, **67**, 202.

Wagner-Jauregg, T., and Hackley, B. E. (1953). *J. Amer. chem. Soc.*, **75**, 2125.

——, ——, Lies, T. A., Owens, O. O., and Proper, R. (1955). *Ibid.*, **77**, 922.

Wills, J. H., Kunkel, A. M., Brown, R. V., and Groblewski, G. E. (1957). *Science*, **125**, 743.

Wilson, I. B. (1952). *J. biol. Chem.*, **199**, 113.

—— (1954). In *A Symposium on the Mechanism of Enzyme Action*, p. 642, ed. W. D. McElroy and B. Glass. John Hopkins Press, Baltimore.

—— (1955). *Disc. Faraday Soc.*, **20**, 119.

—— (1958). *Biochim. Biophys. Acta.*, **27**, 196.

——, and Ginsburg, S. (1955a). *Arch. Biochem.*, **54**, 569.

——, —— (1955b). *Biochim. Biophys. Acta*, **18**, 168.

——, and Meislich, E. K. (1953). *J. Amer. chem. Soc.*, **75**, 4628.

——, and Sondheimer, F. (1957). *Arch. Biochem.*, **69**, 468.

Brit. J. industr. Med., 1959, **16**, 135.

A FOLLOW-UP STUDY OF MEN EXPOSED TO CADMIUM OXIDE FUME

BY

J. A. BONNELL, G. KAZANTZIS, and E. KING

From the Department for Research in Industrial Medicine (Medical Research Council), The London Hospital

(RECEIVED FOR PUBLICATION JUNE 30, 1958)

The results of a follow-up study of 100 men first examined in 1953 after exposure to cadmium oxide fume are presented and discussed.

In 1953 there were 19 cases of chronic cadmium poisoning amongst these men. Twenty-four new cases are now described. The first signs of chronic cadmium poisoning could be seen after a latent interval after exposure had ended. Respiratory function tests showed a greater deterioration in performance with increase in age in the exposed groups compared with the control group. The results in individual cases of clinical and radiological examination and of the respiratory function tests showed a deterioration in the condition of those men with emphysema in the original survey, and took place despite the fact that the majority of the men with chronic cadmium poisoning were not further exposed to cadmium after 1953. Eighteen of the 24 new cases had proteinuria only.

The evidence that chronic cadmium poisoning is associated with renal damage is discussed.

Chronic cadmium poisoning is an insidious disease associated with the development of emphysema and the excretion in the urine of a characteristic protein of low molecular weight. Emphysema and proteinuria may both be present or may occur separately in a particular case (Friberg, 1950; Bonnell, 1955).

In 1953 the health of 100 men exposed to cadmium fume during the manufacture of copper-cadmium alloys at two factories in England was investigated (Bonnell, 1955). As a result of that survey 19 cases of chronic cadmium poisoning were described amongst the men then at work, and four men who were so disabled by their symptoms as to be unable to work were examined in hospital, making a total of 23 cases. Of these 23 men, 11 had emphysema and proteinuria, eight had proteinuria alone, and four had emphysema alone. One man died in uraemia, the result of chronic renal failure.

Reports of further cases of proteinuria at one of these factories led us to undertake a follow-up study of the exposed men in 1957, four years after the original survey. It was hoped to obtain information about the course of the disease, particularly on whether it was self limiting in the absence of further exposure to cadmium, and whether the first symptoms or signs of poisoning could occur after a latent interval.

Method of Investigation

In order to preserve continuity with the initial investigation in 1953 the two factories will be referred to as Factory A and Factory B; the exposed groups at these factories, Group 1A and Group 1B respectively; and individual patients will again be referred to as Case A(n) and Case B(n). All the men comprising Groups 1A and 1B who could be traced were asked to take part in the survey. Each man was interviewed and a clinical examination made. As in the previous survey the occupational history, past medical history, and family history were obtained, and specific enquiry was made about watery discharge from the nose, anosmia, yellow discoloration of the teeth, cough, dyspnoea, and frequency of micturition. At the clinical examination, blood pressure and chest expansion were measured. The haemoglobin concentration, erythrocyte sedimentation rate, haematocrit, and plasma proteins showed no abnormality in 1953 and these estimations were not repeated.

All the men provided early morning specimens of urine and additional specimens were obtained when the men attended for examination: 24-hour specimens were obtained from as many of the workmen as possible. The early morning specimens were tested for specific gravity, sugar, and blood, and all specimens were tested for protein. The methods used were (*a*) the boiling test, (*b*) 25% trichloracetic acid, (*c*) 3% sulphosalicylic acid, and (*d*) "altest" reagent tablets (supplied by Ames Co. Ltd.—active principle sulphosalicylic acid). Esbach's quantitative test was carried out on all urines giving positive results with any one test for protein. Two

methods were used to test for glucose, one of which was a specific qualitative test and the other quantitative. Dipsticks ("clinistix", Ames Co. Ltd.), utilizing an enzymatic reaction, were used on all specimens of urine; a positive reaction is obtained at very high dilutions of glucose and the reaction is specific. All specimens in which a positive reaction was obtained by this method were then tested quantitatively by the "reagent tablet" ("clinitest", Ames Co. Ltd.). The cadmium concentration of each specimen of urine received was estimated by polarography.

The demonstration of protein in the urine is an objective test which can be confirmed by testing repeated specimens of urine. The presence of the characteristic protein in the urine is taken as sufficient evidence for the diagnosis of chronic cadmium poisoning.

Respiratory function tests designed to show impairment of the ventilatory function of the lungs were performed by all the men who attended for examination. The following measurements were made: (*a*) Curves of expiratory fast vital capacity (forced expiratory spirogram, Gandevia and Hugh-Jones, 1957). Three curves were obtained from each subject and the mean time constant determined. (*b*) Maximum ventilatory capacity at 70 respirations per minute ($M.V.C._{70}$) (maximum voluntary ventilation 70, Gandevia and Hugh-Jones, 1957). Two estimations were made, and the mean value determined. (*c*) The swept fraction was determined by expressing the mean tidal excursion in the maximum ventilatory capacity test as a percentage of the vital capacity. (*d*) The vital capacity was taken as the mean of the three expiratory fast vital capacity volumes.

The tests were again performed on the spirometer described by Bernstein, D'Silva, and Mendel (1952), and by the same operator as before. The details of the conduct of the tests and of the measurement of the tracings have already been described (D'Silva, Freeland, and Kazantzis, 1953; D'Silva and Kazantzis, 1954; Kazantzis, 1956).

A new control group was made up of the total complement of men working in the brass foundry in Factory B. There were 63 men in this group. They gave occupational and past medical histories, and all performed the respiratory function tests. The original control groups could no longer be examined, as many of the men had found alternative employment since 1953. All the men seen on this occasion were asked to attend for chest radiographs. As on the previous visit to these factories two postero-anterior chest views were taken of each man, one in full inspiration and one in full expiration.

The chest radiographs were read by two observers who were not aware of the identity of the patient when the radiographs were viewed. The readings were repeated three times using the same technique as before. Thirty-five of the 46 men examined at Factory A and all 37 of the men examined at Factory B attended for chest radiological examination. The radiological findings where relevant are included in the case notes (Appendix 1).

As in the previous investigation independent assessments of the respiratory system were made by clinical examination, radiological examination, and by tests of respiratory function. The diagnosis of emphysema was made by taking into consideration the clinical findings, the radiological findings, and the results of the respiratory function tests. Unless two of these three criteria were satisfied no man was regarded as suffering from emphysema.

The cadmium concentration of the atmosphere in the casting shops at both factories was estimated continuously over a period of five working days. Two methods were used. (*a*) For quantitative atmosphere sampling a benzamide pad (60 mesh), 1 inch in diameter and 10 mm. in thickness was used as a collecting medium. An Edward's IV pump was used to draw the air through this pad at an air flow rate of 10 litres per minute. It has been our experience that the resistance of the benzamide pad at this rate of air flow is constant, enabling a flow-controlling orifice to be inserted between the pad and the pump. Before reaching the benzamide pad the air passed through an elutriator of the type described by Wright (1954), but designed in this case to remove all the particles of cadmium oxide greater than 7 μ in diameter. (*b*) In addition, a strip recorder was used to establish the times of greatest emission of cadmium oxide fume.

Results

In the two factories 83 of the 100 men who comprised Groups 1A and 1B were re-examined. In all, 24 new cases of chronic cadmium poisoning were discovered, five with emphysema and proteinuria, one with emphysema alone, and 18 with proteinuria alone. Thus of the 100 men first seen in 1953, a total of 43 are now known to have evidence of chronic cadmium poisoning. There were in addition four men whose case records were described by Bonnell (1955), namely, Cases A1, A2, A3, and A4, and two men formerly employed in Factory A and seen for the first time in consultation with their family doctors in May, 1957 (Cases D1 and D2, Appendix 1).

Factory A.—Forty-six of the 58 men who comprised Group 1A attended for examination. Of the 12 absentees, four were known cases of chronic cadmium poisoning, Cases A6, A10, and A13, who were unable to travel to the factory because of severe dyspnoea, and Case A9 who had died of carcinoma of the bronchus. One man refused to attend for a further examination and seven had left the company's employ. Five of these were reported by their general practitioners to be in good health and two could not be traced.

Of the 46 men seen on this occasion in Group 1A, there were 19 cases of chronic cadmium poisoning; 14 were new cases (Table 1) of which five had emphysema and proteinuria, one had emphysema alone, and eight had proteinuria alone; five were old cases of which four had emphysema and proteinuria and one had proteinuria.

Of the 14 new cases, six were still employed in the

TABLE 1

NEW CASES OF CADMIUM POISONING AT FACTORY A

Case No.	Age	Exposure	Symptoms	Clinical Findings	B.P. (mm. Hg)	Urine		Respiratory Function Tests				Chest Radiographs	Diagnosis
						Protein	Cd (μg./l.)	T.C. (sec.)	M.V.C. (l./min.)	S.F.$_{75}$ (%)	V.C. (l.)		
A 24	62	16 years near Cd furnace (1941-57)	Winter cough, dyspnoea	Normal	170/100	+ ve	Cd present (not measurable)	0·96 (0·75)*	145 (141)	43·6 (44·3)	4·75 (4·53)	Normal	Proteinuria
A 17	64	13 years (1940-53)	Joint pain, dyspnoea	Rheumatoid arthritis	130/90	+ ve	30	1·16 (0·94)	93	35·1 (45)	3·77 (3·95)	Emphysema	Emphysema, proteinuria
A 25	52	9 years (1946-55)	Dyspnoea 2 years, cough	Emphysema	130/90	+ ve	30	1·21 (0·84)	76 (112)	46·2 (43·2)	2·34 (3·7)	Apical bullae	Emphysema, proteinuria
A 26	51	21 years near Cd. furnace (1936-57)	None	Normal	160/70	+ ve	10	0·62 (0·45)	173 (145·5)	66 (50)	3·75 (4·12)	Normal	Proteinuria
A 27	52	10 years (1947-57)	None	Normal	170/100	+ ve	10	0·69 (0·57)	125 (127)	43 (44)	4·18 (4·12)	Normal	Proteinuria
A 28	48	13 years (1944-57)	Dyspnoea on effort; soreness of nose with occasional epistaxis	Normal	150/100	+ ve	60	0·82 (0·54)	140 (160)	45 (45)	4·50 (5·09)	Normal	Proteinuria
A 29	59	17 years near Cd furnace (1936-53)	Dyspnoea on effort	Obesity, benign hypertension	210/100	+ ve	Cd present (not measurable)	0·74 (0·59)	99 (110·4)	41 (40)	3·45 (3·95)	Normal	Proteinuria
A 30	61	20 years near Cd furnace (1936-56)	Dyspnoea on effort, pains	Obesity, osteoarthritis lower limbs	130/90	+ ve	18	0·77 (0·56)	125	45·8	3·90 (3·61)	Not radiographed	Proteinuria
A 31	53	21 years (1936-57)	Dyspnoea on effort	Emphysema	140/90	+ ve	60	1·10 (0·63)	143·5 (133·3)	51·1 (49·1)	4·0 (3·88)	Emphysema	Emphysema, proteinuria
A 32	29	9 years near Cd furnace (1942-53)	None	Normal	130/90	+ ve	10	0·41 (0·28)	151·2 (185·6)	55·5 (69·0)	3·89 (3·84)	Normal	Proteinuria
A 33	51	15 years near Cd furnace (1936-51)	Dyspnoea on effort	Obesity, bronchospasm	160/90	+ ve	No cadmium	0·42 (0·36)	109·5 (113·6)	44·4 (45·1)	3·53 (3·60)	Normal	Proteinuria
A 34	67	20 years near Cd furnace (1936-56)	Cough with sputum 2 years, dyspnoea on effort 1 year, pain in joints 3 years	Emphysema, chronic bronchitis	160/90	+ ve	14	1·30 (0·83)	44·7 (123·5)	17·9 (41·0)	3·57 (4·30)	Not radiographed	Emphysema, proteinuria
A 35	56	35 years (1920-55)	Dyspnoea and cough	Emphysema, bronchitis	150/100	+ ve	9	1·21 (0·68)	81·0 (125·9)	28·3 (39·5)	4·09 (4·56)	Normal	Emphysema, proteinuria
A 36	46	21 years (1936-57)	Occasional dyspnoea on effort	Emphysema, bronchospasm	110/80	Normal	Cd present (not measurable)	1·28 (0·83)	95·6 (118·6)	35·7 (45·6)	3·82 (3·71)	Normal	Emphysema

*Figures in brackets refer to 1953 results.

casting shop, four on the copper-cadmium furnaces, and two in the vicinity casting brass and bronze; they had done this work for between 10 and 21 years. Eight had left the casting shop at some time between 1951 and 1956; their period of service in the casting shop varied between nine and 35 years. Two had retired (Cases A30 and A34), one because of arthritis and the other because of dyspnoea and arthritis; the remaining six worked in different departments in the factory. Case A17 because of rheumatoid arthritis and Case A35 because of cough and dyspnoea. All 14 of these men were normal at the time of the investigation in 1953. Four of these men (Cases A17, A29, A32, A33) had stopped working in the casting shop before that date so that they had not been further exposed to cadmium in the interim period.

At this factory nine cases of chronic cadmium poisoning were known to exist amongst the 58 men originally in the exposed group. There were in addition four men whose case records were summarized by Bonnell in 1955 (Cases A1, A2, A3, and A4).

Of these 13 men, Case A1 died from chronic renal failure (Bonnell, 1955), Case A4 died at home in 1955 of congestive cardiac failure as the result of emphysema, and Case A9 died at home in 1956 of bronchogenic carcinoma; unfortunately no necropsies were performed on the latter two cases. Cases A2 and A3 were seen and in both the symptoms had become so severe that disability was complete; they were unable to leave their homes unless taken by motor car. On clinical examination both had severe emphysema, protein was present in the urine, and the respiratory function tests were grossly abnormal. Both men were excreting cadmium in the urine, Case A2, 60 μg. of cadmium per litre, Case A3, 36 μg. of cadmium per litre. Five of the remaining eight men were re-examined and the relevant follow-up notes are included in Appendix I.

The remaining three known cases of chronic cadmium poisoning were not examined, but it was ascertained from the general practitioners concerned that Cases A6 and A13 were severely disabled as the result of shortness of breath; Case A6 had

TABLE 2
NEW CASES OF CADMIUM POISONING AT FACTORY B

Case No.	Age	Exposure	Symptoms	Clinical Findings	B.P. (mm. Hg)	Urine		Respiratory Function Tests				Chest Radiographs	Diagnosis
						Protein	Cd (μg./l.)	T.C. (sec.)	M.V.C. (l./min.)	$S.F_{.75}$ (%)	V.C. (l.)		
B 11	42	18 years (1939-57)	Dyspnoea 3 years, cough 3 years	Normal chest	150/80	+ ve	28	0·73 (0·60)*	84·8 (92·6)	26·4 (28·5)	4·58 (4·62)	Normal	Proteinuria
B 16	50	5 years (1945-50)	Chronic nasal discharge	Normal chest	130/90	+ ve	46	0·55 (0·43)	181·3 (195·9)	59·2 (60·0)	4·37 (4·66)	Normal	Proteinuria
B 17	44	18 years (1939-57) Crane driver: situated over CuCd furnaces	None	Normal chest	140/90	+ ve	No Cd	160·4 (0·63)	160·4 (205·0)	39·8 (53·3)	5·57 (5·52)	Normal	Proteinuria
B 18	41	7 years (between 1935-45)	None	Refused clinical examination	—	+ ve	No Cd	0·55 (0·40)	165·8 (189·0)	62·3 (62·7)	3·80 (4·30)	Normal	Proteinuria
B 33	62	7 years (1940-47)	Cough, sputum, dyspnoea 3 years	Chronic bronchitis	160/90	+ ve	No Cd	0·71 (0·48)	61·7 (106·5)	35·6 (52·9)	2·48 (2·88)	Normal	Proteinuria
B 19	49	16 years (1941-57)	None	Normal	140/90	+ ve	40	0·48 (0·45)	150·4 (149·7)	57·4 (53·2)	3·75 (4·02)	Normal	Proteinuria
B 31	64	14 years (1936-50) (intermittent)	Dyspnoea on effort 6 years	Very small man, otherwise normal chest	190/100	+ ve	38	0·39 (0·34)	92·6 (97·2)	81·1 (51·2)	1·63 (2·70)	Normal	Proteinuria
B 20	53	11 years (1946-57)	Dyspnoea on effort 4 years, cough 6 years	Normal chest	130/90	+ ve	110	0·74 (0·54)	100·3 (119·6)	44·8 (48·6)	3·20 (3·50)	Normal	Proteinuria
B 21	47	5 years (between 1940-47)	Dyspnoea on effort 3 years, cough 2 years	Normal chest	130/80	+ ve	Cd present (not measurable)	1·08 (0·96)	96·4 (120·3)	32·6 (37·1)	4·22 (4·62)	Normal	Proteinuria
B 22	52	3 years (1939-42)	Symptom free	(Information gained from family doctor)		+ ve	Cd present (not measurable)	—	—	—	—	—	Proteinuria

*Figures in brackets refer to 1953 results.

emphysema and congestive cardiac failure and Case A13 had emphysema. A specimen of urine from the former was now shown to contain protein. Case A10 was able to continue at work.

In the previous investigation (King, 1955) atmospheric samples were taken from two positions in the casting shop, one near the pit furnace where the master alloy was manufactured, position A, and one near the rocker furnace, position B. On this occasion all samples were taken from position B only. Samples were taken on nine consecutive periods of 12 hours each in order to estimate the average concentration during this time. On no occasion did the concentration of cadmium in the atmosphere exceed 37 $\mu g./m^3$ for any one nine-hour period and the average concentration for the week was 13 $\mu g./m^3$. The results compare favourably with those reported in 1953 when the range of atmosphere concentration was 13 to 89 $\mu g./m^3$ in 12-hour periods. The better conditions had been achieved by improved exhaust ventilation over the rocker furnace. The trace obtained on the strip recorder suggested that part at least of the general concentration of cadmium in the atmosphere was due to occasional bad positioning of the exhaust hood by a particular furnace man.

Factory B.—Thirty-seven of the 42 men originally in Group 1B attended for examination. Of the five absentees one man known to have chronic cadmium posioning had died (Case B3). The other four were traced through their general practitioners; three were in apparent good health and one was found to have the characteristic proteinuria. Of the 37 men seen at the factory, 18 showed signs of chronic cadmium poisoning. There are therefore 19 cases to be discussed. Of these, 10 were new cases all with proteinuria (Table 2) and nine were old cases, four with emphysema and proteinuria, four with proteinuria alone, and one with emphysema alone.

Of the 10 new cases, four continued to work on the copper-cadmium furnaces; they had done this work for between 11 and 18 years. The other six had not been exposed to cadmium in their work for at least seven years. These 10 men were examined in 1953 and found to be quite normal.

In addition, three men who had been shown to have proteinuria on one occasion by Kench and Smith (1957) provided repeated specimens of urine but the proteinuria could not be demonstrated unequivocally. Quantitative protein estimation by the Biuret method was carried out on one occasion and the protein content varied between 3·5 and 5·5 mg. total protein per 100 ml. of urine. It is possible that the proteinuria is transient when it first appears. Should that be so, careful observation and repeated testing of the urine would show the onset of persistent proteinuria in these cases.

At this factory 10 cases of chronic cadmium

poisoning were known to exist amongst the 42 men originally in the exposed group (Group 1B, Bonnell, 1955). The findings at that time were summarized in table form and the case history of one man who was severely disabled (Case B1) was described in full. Of these 10 men, one (Case B3) had died of acute bronchopneumonia and the post-mortem findings have been reported by Kench and Smith (1957). The remaining nine men were re-examined in the present investigation and the relevant follow-up notes are included in Appendix 1.

Master Alloy Manufacture.—The master alloy (50/50 copper-cadmium) was manufactured in a separate building from the main casting shop where the low percentage (1%) copper-cadmium alloys were cast. Atmospheric samples were taken in both workshops.

A direct comparison with conditions existing at the time of the previous investigation (King, 1955) was impossible owing to improvements in the exhaust system and pouring technique. The atmospheric samples were taken at a position nearer to the furnacemen than on the previous occasion. For a period of 10 hours of master alloy casting the average concentration of cadmium was 30 μg./m^3. During the process of mixing and pouring, the furnacemen wore Siebe Gorman microfilter dust respirators, the efficiency of which is discussed in Appendix 2.

Final Alloy Manufacture.—Atmospheric samples were taken at two positions comparable to points F and G in the previous investigation for eight consecutive 12-hour periods. The results are summarized in Table 3.

TABLE 3

RESULTS OF ATMOSPHERE SAMPLING AT FACTORY B

Position F	Range 18-80 μg. Cd/m^3 (29-270 μg. Cd/^{3}) Average 46 μg Cd/m^3 (106 μg./m^3)
Position G	Range 10-41 μg. Cd/m^3 (5-56 μg./m^3) Average 20 μg. Cd/m^3 (38 μg./m^3)

Figures in brackets refer to previous report (King, 1955).

These data suggest that the working conditions have improved since the earlier survey. At that time additional amounts of cadmium could have been absorbed by the workman as the result of working close to the furnaces during mixing and pouring operations. In 1957 Siebe Gorman microfilter respirators were worn by the furnacemen during these operations and the atmospheric concentrations probably represent maximum exposure.

Cadmium Content of Respirator Pads.—The exposure of the men to cadmium fume depended to a great extent on their care when working near the source of the fume. The working technique and the variable nature of the fume emission caused serious difficulties when attempting to assess accurately the degree of exposure of an individual workman. This problem was reduced by the use of efficient dust respirators, but the cadmium content of the filter pads after use gave a measure of the possible exposure of an individual under the conditions observed at this factory.

The filter pads from the respirators used by the furnacemen during each casting operation were collected and their cadmium content estimated (Table 4).

TABLE 4

CADMIUM CONTENT OF FILTER PADS OF RESPIRATORS

	Master Alloy Casting	Final Alloy Casting
	12 filters obtained from 2 furnacemen	20 filters obtained from 7 workmen
Average time of use	9 min.	20 min.
Average cadmium content	0·14 mg.	0·5 mg.
Range of cadmium content	0·05—0·31 mg.	0·08—3·65 mg.

In this series three of the four highest values were from the pads supplied by one workman (Case B20). It is interesting to note that this man's urinary excretion of cadmium was far higher than that of any of his workmates (Table 2).

These data give the total cadmium content of the air inhaled by the workmen concerned, and include the large non-respirable particles of cadmium oxide or particles of mixed oxides from sparks. They do, however, demonstrate the possible variation in exposure of workmen performing essentially the same work under the same conditions.

Results of Respiratory Function Tests

The number of men examined on this occasion and the mean ages of the groups are shown in Table 5. The table also shows the mean values in the three groups for vital capacity, maximum ventilatory capacity, swept fraction, and time constant of the expiratory fast vital capacity curve. The corresponding mean values obtained four years ago are also shown for comparison. In the exposed groups, the mean values for 1957 were lower than the corresponding values for 1953 for vital capacity, swept fraction, and maximum ventilatory capacity, and higher for time constant. This suggested deterioration in respiratory function. However, the effect of age and the incidence of respiratory disease in the population from which these samples were drawn must be taken into account before any conclusions are drawn as to the effects of exposure to cadmium fume.

TABLE 5

MEAN VALUES AND STANDARD DEVIATIONS FOR THE CONTROL AND EXPOSED GROUPS IN EACH FACTORY

Groups	No. of Subjects		Mean Age		Vital Capacity (litres)		Time Constant (sec.)		Swept Fraction (%)		M.V.C.$_{75}$ (litres/min.)	
	1957	1953	1957	1953	1957	1953	1957	1953	1957	1953	1957	1953
Controls:												
Factory A	—	60	—	49·4 (9·30)*	—	3·99 (0·72)	—	0·59 (0·16)	—	49·3 (7·75)	—	138 (32)
Factory B	63	44	37·7 (13·19)	39·8 (12·00)	4·13 (1·09)	4·46 (0·69)	0·64 (0·18)	0·58 (0·26)	47·3 (9·95)	47·5 (8·35)	136 (37)	148 (29)
Exposed:												
Factory A	45	56	51·4 (9·29)	49·0 (9·96)	3·90 (1·06)	4·12 (1·06)	0·94 (0·48)	0·76 (0·44)	42·7 (10·84)	44·3 (10·75)	121 (47)	130 (47)
Factory B	35	40	45·4 (10·69)	41·4 (10·62)	3·91 (1·07)	4·32 (0·82)	0·97 (0·84)	0·79 (0·63)	45·9 (12·45)	46·2 (12·29)	128 (45)	142 (50)

*Standard deviations are in brackets.

TABLE 6

REGRESSIONS ON AGE FOR VITAL CAPACITY, TIME CONSTANT, SWEPT FRACTION, AND MAXIMUM VENTILATORY CAPACITY IN CONTROL AND EXPOSED GROUPS OF BOTH FACTORIES, WITH A COMPARISON BETWEEN SLOPES OF REGRESSION LINES

Test	Group	Regression Equation	S.E.b	Difference in Slope between	t	P
V.C.	Control:					
	1957 (B)	$y = 5{\cdot}92 - 0{\cdot}047x$	0·0087	1957 and 1953 controls	1·46	$0{\cdot}2 > P > 0{\cdot}1$
	1953 (B)	$y = 5{\cdot}68 - 0{\cdot}031x$	0·0075			
	Exposed:					
	1957 (A)	$y = 7{\cdot}29 - 0{\cdot}066x$	0.014	1957 Control and exposed	1·14	$0{\cdot}3 > P > 0{\cdot}2$
	1957 (B)	$y = 6{\cdot}75 - 0{\cdot}063x$	0·014	1957 Control and exposed	0·95	$0{\cdot}4 > P > 0{\cdot}2$
T.C.	Control:					
	1957 (B)	$y = 0{\cdot}58 + 0{\cdot}0014x$	0·0017	1957 and 1953 controls	0·04	$P > 0{\cdot}9$
	1953 (B)	$y = 0{\cdot}52 + 0{\cdot}0015x$	0·0033			
	Exposed:					
	1957 (A)	$y = 0{\cdot}02 + 0{\cdot}018x$	0·0074	1957 Control and exposed	2·17	$0{\cdot}05 > P > 0{\cdot}02$
	1957 (B)	$y = -0{\cdot}46 + 0{\cdot}031x$	0·012	1957 Control and exposed	2·40	$0{\cdot}02 > P > 0{\cdot}01$
S.F.$_{75}$	Control:					
	1957 (B)	$y = 45{\cdot}0 + 0{\cdot}062x$	0·096	1957 and 1953 controls	0·91	$0{\cdot}4 > P > 0{\cdot}3$
	1957 (B)	$y = 50{\cdot}3 - 0{\cdot}069x$	0·11			
	Exposed:					
	1957 (A)	$y = 69{\cdot}7 - 0{\cdot}53x$	0·16	1957 Control and exposed	3·14	$P < 0{\cdot}01$
	1957 (B)	$y = 60{\cdot}2 - 0{\cdot}32x$	0.20	1957 Control and exposed	1·72	$0{\cdot}1 > P > 0{\cdot}05$
M.V.C.$_{75}$	Control:					
	1957 (B)	$y = 185{\cdot}9 - 1{\cdot}33x$	0·31	1957 and 1953 controls	0·29	$0{\cdot}8 > P > 0{\cdot}7$
	1953 (B)	$y = 195{\cdot}4 - 1{\cdot}20x$	0·32			
	Exposed:					
	1957 (A)	$y = 283{\cdot}4 - 3{\cdot}17x$	0·62	1957 Control and exposed	2·64	$0{\cdot}02 > P > 0{\cdot}01$
	1957 (B)	$y = 255{\cdot}8 - 2{\cdot}81x$	0·56	1957 Control and exposed	2·29	$0{\cdot}05 > P > 0.02$

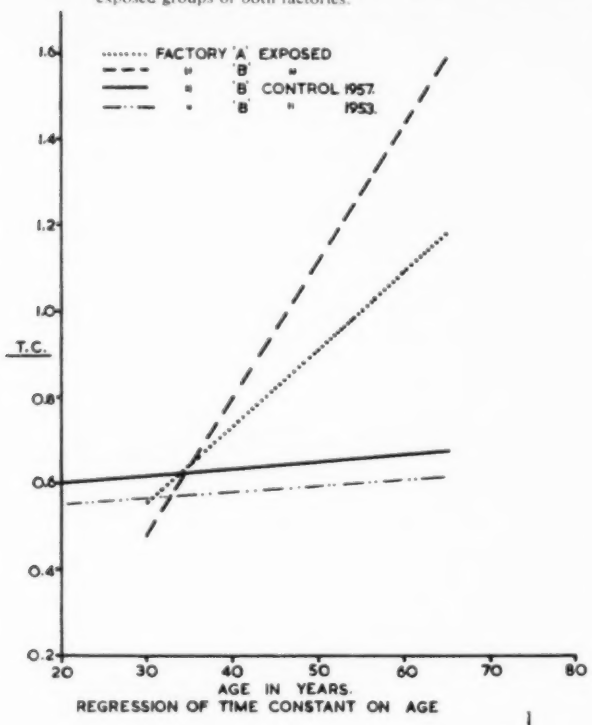
Comparison of Control Groups in 1953 and 1957.—The regression on age was calculated for each of the variables measured in the present control group. It was ascertained that this relationship could be assumed to be linear over the age-range studied (Armitage, 1955). These regression equations are shown in Table 6. The regression lines obtained were then compared for both slope and position with the corresponding regression lines obtained in the 1953 control group in Factory B.

No significant differences were shown to exist between these two control groups in the slope of the regression lines for time constant, M.V.C., vital capacity, or swept fraction (Table 6). For the time constant, the results in the two control groups were close, there being no significant difference in slope or in position of the two regression lines (Fig. 1). For the vital capacity and M.V.C., the regression on age was similar in the two groups but the distance apart of the regression lines was significant, the 1957 values being lower than the 1953 values.

Comparison between Present Control and Exposed Groups.—This comparison was effected by the same technique of fitting linear regression lines to the available data. The regression equations obtained for the exposed groups in both factories are shown in Table 6.

Significant differences between the control and exposed groups were obtained for time constant, swept fraction, and maximum ventilatory capacity. It can be seen that in the exposed groups the maximum ventilatory capacity decreased at a greater rate with increase in age, and the time constant of the expiratory fast vital capacity curve increased at a greater rate with age. The regression lines representing

FIG. 1.—Regression of time constant on age in the control and exposed groups of both factories.



these equations for the time constant in the control and exposed groups are shown diagrammatically in Fig. 1. The swept fractions were also found to decrease at a greater rate in the exposed groups with increase in age, although the difference between the exposed group in Factory B and the control group does not reach the 5% level of significance. No significant difference could be found between the control and exposed groups in the rate at which the vital capacity decrease with increase in age.

Comparison between 1953 and 1957 Exposed Groups.—Fig. 2 shows the individual values for time constant for 1957 plotted against the respective values for 1953. The majority of values for time constant were higher in 1957, suggesting a deterioration of respiratory function. In the absence of a follow-up study of the original control group it was difficult to attribute the deterioration in respiratory function to factors other than the increase in age and the expected incidence of respiratory disease in the population from which this sample was drawn.

The expected change in each of the tests over a period of four years was calculated from the regression equations based on the present controls. The difference between the 1957 and 1953 performance of the exposed group was adjusted by this amount, so that any residual difference could be attributed to some factor other than the expected deterioration due to increase in age. These residual differences were tested to see whether they were significantly different from zero, allowance having been made for the scatter of the observations about the regression line of the control subjects. For time constant these residual differences were highly significant; they were also significantly different from zero for the M.V.C., suggesting that the deterioration in these quantities over four years was greater than could be expected on the basis of age alone. For vital capacity and swept fraction, the residual differences were not significantly different from zero (Table 7). For the purposes of this analysis, only those subjects working at the time of the survey were included in the exposed

FIG. 2.—Comparison of individual time constants in 1953 and 1957 in the exposed groups of both factories.

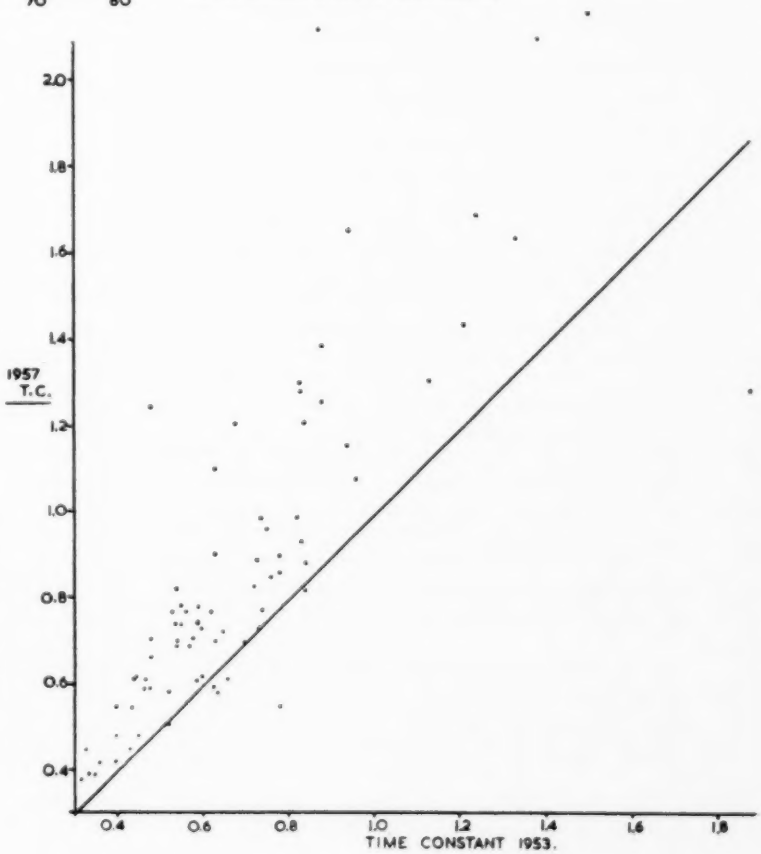


TABLE 5

MEAN VALUES AND STANDARD DEVIATIONS FOR THE CONTROL AND EXPOSED GROUPS IN EACH FACTORY

Groups	No. of Subjects		Mean Age		Vital Capacity (litres)		Time Constant (sec.)		Swept Fraction (%)		M.V.C.$_{\cdot 70}$ (litres/min.)	
	1957	1953	1957	1953	1957	1953	1957	1953	1957	1953	1957	1953
Controls:												
Factory A	—	60	—	49·4 (9·30)*	—	3·99 (0·72)	—	0·59 (0·16)	—	49·3 (7·75)	—	138 (32)
Factory B	63	44	37·7 (13·19)	39·8 (12·00)	4·13 (1·09)	4·46 (0·69)	0·64 (0·18)	0·58 (0·26)	47·3 (9·95)	47·5 (8·35)	136 (37)	148 (29)
Exposed:												
Factory A	45	56	51·4 (9·29)	49·0 (9·96)	3·90 (1·06)	4·12 (1·06)	0·94 (0·48)	0·76 (0·44)	42·7 (10·84)	44·3 (10·75)	121 (47)	130 (47)
Factory B	35	40	45·4 (10·69)	41·4 (10·62)	3·91 (1·07)	4·32 (0·82)	0·97 (0·84)	0·79 (0·63)	45·9 (12·45)	46·2 (12·29)	128 (45)	142 (50)

*Standard deviations are in brackets.

TABLE 6

REGRESSIONS ON AGE FOR VITAL CAPACITY, TIME CONSTANT, SWEPT FRACTION, AND MAXIMUM VENTILATORY CAPACITY IN CONTROL AND EXPOSED GROUPS OF BOTH FACTORIES, WITH A COMPARISON BETWEEN SLOPES OF REGRESSION LINES

Test	Group	Regression Equation	S.E.b	Difference in Slope between	t	P
V.C.	Control:					
	1957 (B)	$y = 5{\cdot}92 - 0{\cdot}047x$	0·0087	1957 and 1953 controls	1·46	$0{\cdot}2 > P > 0{\cdot}1$
	1953 (B)	$y = 5{\cdot}68 - 0{\cdot}031x$	0·0075			
	Exposed:					
	1957 (A)	$y = 7{\cdot}29 - 0{\cdot}066x$	0.014	1957 Control and exposed	1·14	$0{\cdot}3 > P > 0{\cdot}2$
	1957 (B)	$y = 6{\cdot}75 - 0{\cdot}063x$	0·014	1957 Control and exposed	0·95	$0{\cdot}4 > P > 0{\cdot}2$
T.C.	Control:					
	1957 (B)	$y = 0{\cdot}58 + 0{\cdot}0014x$	0·0017	1957 and 1953 controls	0·04	$P > 0{\cdot}9$
	1953 (B)	$y = 0{\cdot}52 + 0{\cdot}0015x$	0·0033			
	Exposed:					
	1957 (A)	$y = 0{\cdot}02 + 0{\cdot}018x$	0·0074	1957 Control and exposed	2·17	$0{\cdot}05 > P > 0{\cdot}02$
	1957 (B)	$y = -0{\cdot}46 + 0{\cdot}031x$	0·012	1957 Control and exposed	2·40	$0{\cdot}02 > P > 0{\cdot}01$
S.F.$_{\cdot 70}$	Control:					
	1957 (B)	$y = 45{\cdot}0 + 0{\cdot}062x$	0·096	1957 and 1953 controls	0·91	$0{\cdot}4 > P > 0{\cdot}3$
	1957 (B)	$y = 50{\cdot}3 - 0{\cdot}069x$	0·11			
	Exposed:					
	1957 (A)	$y = 69{\cdot}7 - 0{\cdot}53x$	0·16	1957 Control and exposed	3·14	$P < 0{\cdot}01$
	1957 (B)	$y = 60{\cdot}2 - 0{\cdot}32x$	0.20	1957 Control and exposed	1·72	$0{\cdot}1 > P > 0{\cdot}05$
M.V.C.$_{\cdot 70}$	Control:					
	1957 (B)	$y = 185{\cdot}9 - 1{\cdot}33x$	0·31	1957 and 1953 controls	0·29	$0{\cdot}8 > P > 0{\cdot}7$
	1953 (B)	$y = 195{\cdot}4 - 1{\cdot}20x$	0·32			
	Exposed:					
	1957 (A)	$y = 283{\cdot}4 - 3{\cdot}17x$	0·62	1957 Control and exposed	2·64	$0{\cdot}02 > P > 0{\cdot}01$
	1957 (B)	$y = 255{\cdot}8 - 2{\cdot}81x$	0·56	1957 Control and exposed	2·29	$0{\cdot}05 > P > 0{\cdot}02$

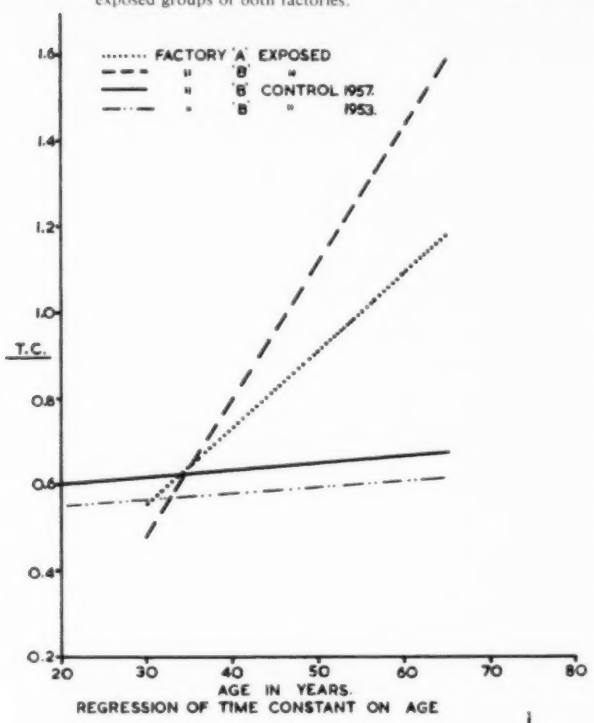
Comparison of Control Groups in 1953 and 1957.—The regression on age was calculated for each of the variables measured in the present control group. It was ascertained that this relationship could be assumed to be linear over the age-range studied (Armitage, 1955). These regression equations are shown in Table 6. The regression lines obtained were then compared for both slope and position with the corresponding regression lines obtained in the 1953 control group in Factory B.

No significant differences were shown to exist between these two control groups in the slope of the regression lines for time constant, M.V.C., vital capacity, or swept fraction (Table 6). For the time constant, the results in the two control groups were close, there being no significant difference in slope or in position of the two regression lines (Fig. 1). For the vital capacity and M.V.C., the regression on age was similar in the two groups but the distance apart of the regression lines was significant, the 1957 values being lower than the 1953 values.

Comparison between Present Control and Exposed Groups.—This comparison was effected by the same technique of fitting linear regression lines to the available data. The regression equations obtained for the exposed groups in both factories are shown in Table 6.

Significant differences between the control and exposed groups were obtained for time constant, swept fraction, and maximum ventilatory capacity. It can be seen that in the exposed groups the maximum ventilatory capacity decreased at a greater rate with increase in age, and the time constant of the expiratory fast vital capacity curve increased at a greater rate with age. The regression lines representing

FIG. 1.—Regression of time constant on age in the control and exposed groups of both factories.



these equations for the time constant in the control and exposed groups are shown diagrammatically in Fig. 1. The swept fractions were also found to decrease at a greater rate in the exposed groups with increase in age, although the difference between the exposed group in Factory B and the control group does not reach the 5% level of significance. No significant difference could be found between the control and exposed groups in the rate at which the vital capacity decrease with increase in age.

Comparison between 1953 and 1957 Exposed Groups.—Fig. 2 shows the individual values for time constant for 1957 plotted against the respective values for 1953. The majority of values for time constant were higher in 1957, suggesting a deterioration of respiratory function. In the absence of a follow-up study of the original control group it was difficult to attribute the deterioration in respiratory function to factors other than the increase in age and the expected incidence of respiratory disease in the population from which this sample was drawn.

The expected change in each of the tests over a period of four years was calculated from the regression equations based on the present controls. The difference between the 1957 and 1953 performance of the exposed group was adjusted by this amount, so that any residual difference could be attributed to some factor other than the expected deterioration due to increase in age. These residual differences were tested to see whether they were significantly different from zero, allowance having been made for the scatter of the observations about the regression line of the control subjects. For time constant these residual differences were highly significant; they were also significantly different from zero for the M.V.C., suggesting that the deterioration in these quantities over four years was greater than could be expected on the basis of age alone. For vital capacity and swept fraction, the residual differences were not significantly different from zero (Table 7). For the purposes of this analysis, only those subjects working at the time of the survey were included in the exposed

FIG. 2.—Comparison of individual time constants in 1953 and 1957 in the exposed groups of both factories.

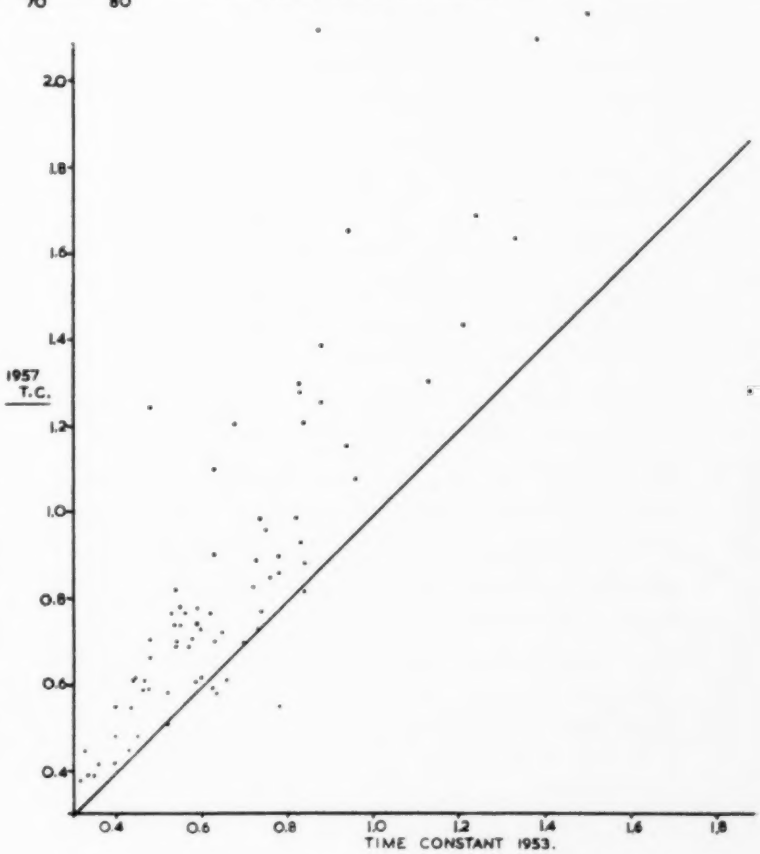


TABLE 7

SIGNIFICANCE OF MEAN DIFFERENCES BETWEEN 1953 AND 1957 RESULTS

Test	Mean Residual Difference	t	P
V.C.	+ 0·126	1·0	0·4 > P > 0·3
T.C.	+ 0·181	5·0	0·0 < P < 0·001
S.F.	+ 2·16	1·4	0·2 > P > 0·1
M.V.C.	+ 11·18	2·5	0·02 > P > 0·01

group. In this way the control and exposed groups were made comparable. The significant differences shown in Table 7 were obtained despite the fact that the results of the men not at work, *i.e.*, the most severely affected members of the exposed group, were not included.

From these results, it was concluded that the deterioration in performance over four years was significantly greater than could be expected from the behaviour of the control group studied.

Individual Performances.—In the initial investigation four years ago limits of normality for swept fraction and time constant were defined, which were based on the performance of the control group in each factory. Men with a swept fraction less than twice the standard deviation from the mean or a time constant greater than twice the standard deviation from the mean were selected for comparison with clinical and radiological findings. In the present investigation the same values for the limits of normality were adopted in order that results might be compared.

Of the 21 men who gave abnormal results in 1953, two have died (A4, B3) and have been considered elsewhere in this paper. Four men from Factory A had left the company's employ and were not re-examined (A10, A13, A14, A18). It was ascertained that two of these men were suffering from shortness of breath. The remaining 15 men again had values for swept fraction or time constant outside the described limits. These values are shown in Table 8.

In the 1957 survey an additional 11 men had abnormal respiratory function tests; in four men both the swept fraction and the time constant were abnormal, in six men only the time constant and in one man only the swept fraction were abnormal (Table 8). Of the 10 men whose time constants were greater than two standard deviations from the mean for the first time in 1957, there were seven whose time constants fell between one and two standard deviations from the mean in 1953.

TABLE 8

SWEPT FRACTIONS AND TIME CONSTANTS FALLING OUTSIDE TWICE THE STANDARD DEVIATION OF THE MEAN FOR CONTROL GROUP IN FACTORIES A AND B

Case No.	Age	T.C. >0·91 sec.*	$S.F._{\cdot 75}$ <34%*
A2	56	2·59	22·4
A3	62	3·05	22·2
A5	62	1·28	Did not perform
A8	59	1·44	33·0
A11	69	2·12	28·7
A12	58	2·95	15·2
A15	49	1·69	29·3
A16	54	1·31	—
A17	64	1·16	—
A20	44	1·26	—
A24	62	0·96	—
A25	52	1·21	—
A31	53	1·10	—
A34	67	1·30	17·9
A35	56	1·21	28·3
A36	46	1·28	—
A37	34	1·39	31·7
A38	47	1·25	—
A39	56	0·93	—
A40	60	—	27·3
B1	56	4·55	Did not perform
B2	53	1·64	—
B4	61	2·10	27·4
B5	63	2·17	30·4
B6	54	3·15	21·2
B11	42	—	26·4

Subjects A11 and A24 to A40 gave values within the normal limits in the initial survey.

*2 S.D.s from control mean.

Results of Examination of Urine

Nine of the 46 men in Factory A were found to give a consistently positive test for glucose in the urine. Ten of the 37 men in Factory B gave positive results with the same test. This slight degree of glycosuria was consistently present in repeated specimens of urine. Two men at Factory B (Cases B2 and B4) were found to have 0·25% and 1% respectively of glucose in the urine. Both these men had typical mild diabetic glucose tolerance curves. Seven of the nine men exhibiting glycosuria in Factory A also had proteinuria and all 10 of the men at Factory B with glycosuria also had proteinuria.

The results of analysis of cadmium excretion in the urine are given in Tables 1 and 2. No correlation was found between the excretion of cadmium in 24-hour specimens and the excretion in spot specimens of urine.

Urinary cadmium excretion in the control group was not studied on this occasion. Bonnell (1955) gave data of a similar control group of 89 men, 76 of whom were not excreting detectable amounts of cadmium, 10 were excreting 10/30 μg. of cadmium per day, and three were excreting over 30 μg. per day. On that occasion the polarographic technique used had a similar sensitivity, *i.e.*, 10 μg. cadmium per litre of urine, to that used in the survey now reported. Smith and Kench (1957) found a similar distribution amongst the 28 subjects in their control group.

As in 1953 questioning did not reveal evidence of watery discharge from the nose or loss of the sense of smell. It was impossible to assess whether a

yellow discoloration of the teeth was present owing to the poor oral hygiene in the majority of the workers. The blood pressure readings were not higher than in the control groups; in fact they were almost identical in individual workmen after a four-year interval. No cadmium was detected in the blood obtained by venepuncture.

Discussion

It is clear from the evidence obtained as the result of this investigation that the first sign of chronic cadmium poisoning can occur after a long latent interval following cessation of exposure to cadmium. When signs or symptoms of poisoning are present, the disease progresses in severity with time and this deterioration occurs in the absence of further exposure to cadmium.

It can be seen from Table 2 that six of the 10 new cases at Factory B had ceased to be exposed to cadmium by 1950. One of these men had only been exposed for three years, from 1939 to 1942. All were normal on examination during the survey carried out at this factory in 1953 (Bonnell, 1955). At Factory A four of the 14 new cases had their last exposure in 1953. Since working conditions were good in 1957, as evidenced by the environmental study, it is unlikely that any of the 24 new cases were due to absorption of cadmium in the period 1953 to 1957.

The men diagnosed as having chronic cadmium poisoning in 1953 showed evidence of deterioration. Three had died (Cases A4, A9, and B3), two as the result of respiratory disease and one of bronchogenic carcinoma. At Factory A only two of the known cases of chronic cadmium poisoning were still at work (Cases A7 and A8), and in one of these (Case A8) there was undoubted evidence of increased severity of the disease. One man (Case A6) who had emphysema only in 1953 had become completely disabled and for the first time had proteinuria. At Factory B only four of the 10 men known to have chronic cadmium poisoning continued at their usual work in the casting shop. Deterioration was demonstrated by clinical examination and respiratory function tests in the remaining six men. One was completely disabled, another was only capable of carrying out sedentary work, and four were only able to do light work.

The results of the respiratory function tests showed a deterioration with increase in age in the exposed groups compared with the control group.

A new group of involuntary controls was investigated at one of the factories; the results are comparable with those obtained in volunteer control groups in 1953, thus validating the original control series and verifying that the procedure adopted in 1957 did not vary significantly from that adopted in 1953.

The measurement of the time constant of the expiratory fast vital capacity curve gave unequivocal results. No difference could be demonstrated between the performance of the 1953 and 1957 control groups, as shown by the similarity of the regression equations on age in each group. However, there was a significant difference between the 1957 control group and the exposed groups in each factory. This difference is well illustrated in Fig. 1. The results for the $M.V.C._{\cdot 70}$ and for the swept fraction support these findings. No useful conclusion could be drawn from the vital capacity results in this any more than in the initial survey. The expiratory fast vital capacity curve provided a reliable and sensitive index of ventilatory function.

The comparison between the exposed groups in 1953 and 1957 showed a greater deterioration than could be expected from the behaviour of the control groups studied. The deterioration over four years in the control group was calculated from observations made on a single occasion. The 1957 investigation was handicapped in this respect because the original control group was not available for examination.

In assessing the respiratory function of individuals, the results of these tests corresponded well with clinical and radiological findings. In a number of cases men who gave abnormal results on this survey gave readings which were close to the normal limits four years previously. It would be of interest to repeat these tests after a further period on men whose results were for the first time close to the normal limits.

The radiological findings agreed closely with the clinical findings and the results of the respiratory function tests. The chest radiographs were inspected without any knowledge of the clinical findings so that an unbiased opinion could be taken of each chest film.

All 10 new cases at Factory B and eight of the 14 new cases at Factory A had proteinuria only. It has been established that the proteinuria in the new cases is identical with that described by Kekwick (1955). Spectrophotometric examination of the urinary proteins gave extinction values at 280 mμ, in the range found for proteins, providing additional evidence that they are protein in nature. Estimation of the bound carbohydrate of these proteins by the method of Sørensen and Haugaard (1933) on three samples of the proteins gave the following values, 18·2%, 22·3%, 29·5%. These figures indicate that these are mucoproteins with a high polysaccharide content and this is consistent with their reaction to sulphosalicylic acid (Kekwick, 1957).

TABLE 7

SIGNIFICANCE OF MEAN DIFFERENCES BETWEEN 1953 AND 1957 RESULTS

Test	Mean Residual Difference	t	P
V.C.	+ 0·126	1·0	0·4 > P > 0·3
T.C.	+ 0·181	5·0	0·0 < P < 0·001
S.F.	+ 2·16	1·4	0·2 > P > 0·1
M.V.C.	+ 11·18	2·5	0·02 > P > 0·01

group. In this way the control and exposed groups were made comparable. The significant differences shown in Table 7 were obtained despite the fact that the results of the men not at work, *i.e.*, the most severely affected members of the exposed group, were not included.

From these results, it was concluded that the deterioration in performance over four years was significantly greater than could be expected from the behaviour of the control group studied.

Individual Performances.—In the initial investigation four years ago limits of normality for swept fraction and time constant were defined, which were based on the performance of the control group in each factory. Men with a swept fraction less than twice the standard deviation from the mean or a time constant greater than twice the standard deviation from the mean were selected for comparison with clinical and radiological findings. In the present investigation the same values for the limits of normality were adopted in order that results might be compared.

Of the 21 men who gave abnormal results in 1953, two have died (A4, B3) and have been considered elsewhere in this paper. Four men from Factory A had left the company's employ and were not re-examined (A10, A13, A14, A18). It was ascertained that two of these men were suffering from shortness of breath. The remaining 15 men again had values for swept fraction or time constant outside the described limits. These values are shown in Table 8.

In the 1957 survey an additional 11 men had abnormal respiratory function tests; in four men both the swept fraction and the time constant were abnormal, in six men only the time constant and in one man only the swept fraction were abnormal (Table 8). Of the 10 men whose time constants were greater than two standard deviations from the mean for the first time in 1957, there were seven whose time constants fell between one and two standard deviations from the mean in 1953.

TABLE 8

SWEPT FRACTIONS AND TIME CONSTANTS FALLING OUTSIDE TWICE THE STANDARD DEVIATION OF THE MEAN FOR CONTROL GROUP IN FACTORIES A AND B

Case No.	Age	T.C. >0·91 sec.*	S.F.% <34%*
A2	56	2·59	22·4
A3	62	3·05	22·2
A5	62	1·28	Did not perform
A8	59	1·44	33·0
A11	69	2·12	28·7
A12	58	2·95	15·2
A15	49	1·69	29·3
A16	54	1·31	—
A17	64	1·16	—
A20	44	1·26	—
A24	62	0·96	—
A25	52	1·21	—
A31	53	1·10	—
A34	67	1·30	17·9
A35	56	1·21	28·3
A36	46	1·28	—
A37	34	1·39	31·7
A38	47	1·25	—
A39	56	0·93	—
A40	60	—	27·3
B1	56	4·55	Did not perform
B2	53	1·64	—
B4	61	2·10	27·4
B5	63	2·17	30·4
B6	54	3·15	21·2
B11	42	—	26·4

Subjects A11 and A24 to A40 gave values within the normal limits in the initial survey.
*2 S.D.s from control mean.

Results of Examination of Urine

Nine of the 46 men in Factory A were found to give a consistently positive test for glucose in the urine. Ten of the 37 men in Factory B gave positive results with the same test. This slight degree of glycosuria was consistently present in repeated specimens of urine. Two men at Factory B (Cases B2 and B4) were found to have 0·25% and 1% respectively of glucose in the urine. Both these men had typical mild diabetic glucose tolerance curves. Seven of the nine men exhibiting glycosuria in Factory A also had proteinuria and all 10 of the men at Factory B with glycosuria also had proteinuria.

The results of analysis of cadmium excretion in the urine are given in Tables 1 and 2. No correlation was found between the excretion of cadmium in 24-hour specimens and the excretion in spot specimens of urine.

Urinary cadmium excretion in the control group was not studied on this occasion. Bonnell (1955) gave data of a similar control group of 89 men, 76 of whom were not excreting detectable amounts of cadmium, 10 were excreting 10/30 μg. of cadmium per day, and three were excreting over 30 μg. per day. On that occasion the polarographic technique used had a similar sensitivity, *i.e.*, 10 μg. cadmium per litre of urine, to that used in the survey now reported. Smith and Kench (1957) found a similar distribution amongst the 28 subjects in their control group.

As in 1953 questioning did not reveal evidence of watery discharge from the nose or loss of the sense of smell. It was impossible to assess whether a

yellow discoloration of the teeth was present owing to the poor oral hygiene in the majority of the workers. The blood pressure readings were not higher than in the control groups; in fact they were almost identical in individual workmen after a four-year interval. No cadmium was detected in the blood obtained by venepuncture.

Discussion

It is clear from the evidence obtained as the result of this investigation that the first sign of chronic cadmium poisoning can occur after a long latent interval following cessation of exposure to cadmium. When signs or symptoms of poisoning are present, the disease progresses in severity with time and this deterioration occurs in the absence of further exposure to cadmium.

It can be seen from Table 2 that six of the 10 new cases at Factory B had ceased to be exposed to cadmium by 1950. One of these men had only been exposed for three years, from 1939 to 1942. All were normal on examination during the survey carried out at this factory in 1953 (Bonnell, 1955). At Factory A four of the 14 new cases had their last exposure in 1953. Since working conditions were good in 1957, as evidenced by the environmental study, it is unlikely that any of the 24 new cases were due to absorption of cadmium in the period 1953 to 1957.

The men diagnosed as having chronic cadmium poisoning in 1953 showed evidence of deterioration. Three had died (Cases A4, A9, and B3), two as the result of respiratory disease and one of bronchogenic carcinoma. At Factory A only two of the known cases of chronic cadmium poisoning were still at work (Cases A7 and A8), and in one of these (Case A8) there was undoubted evidence of increased severity of the disease. One man (Case A6) who had emphysema only in 1953 had become completely disabled and for the first time had proteinuria. At Factory B only four of the 10 men known to have chronic cadmium poisoning continued at their usual work in the casting shop. Deterioration was demonstrated by clinical examination and respiratory function tests in the remaining six men. One was completely disabled, another was only capable of carrying out sedentary work, and four were only able to do light work.

The results of the respiratory function tests showed a deterioration with increase in age in the exposed groups compared with the control group.

A new group of involuntary controls was investigated at one of the factories; the results are comparable with those obtained in volunteer control groups in 1953, thus validating the original control series and verifying that the procedure adopted in 1957 did not vary significantly from that adopted in 1953.

The measurement of the time constant of the expiratory fast vital capacity curve gave unequivocal results. No difference could be demonstrated between the performance of the 1953 and 1957 control groups, as shown by the similarity of the regression equations on age in each group. However, there was a significant difference between the 1957 control group and the exposed groups in each factory. This difference is well illustrated in Fig. 1. The results for the $M.V.C._{\cdot 70}$ and for the swept fraction support these findings. No useful conclusion could be drawn from the vital capacity results in this any more than in the initial survey. The expiratory fast vital capacity curve provided a reliable and sensitive index of ventilatory function.

The comparison between the exposed groups in 1953 and 1957 showed a greater deterioration than could be expected from the behaviour of the control groups studied. The deterioration over four years in the control group was calculated from observations made on a single occasion. The 1957 investigation was handicapped in this respect because the original control group was not available for examination.

In assessing the respiratory function of individuals, the results of these tests corresponded well with clinical and radiological findings. In a number of cases men who gave abnormal results on this survey gave readings which were close to the normal limits four years previously. It would be of interest to repeat these tests after a further period on men whose results were for the first time close to the normal limits.

The radiological findings agreed closely with the clinical findings and the results of the respiratory function tests. The chest radiographs were inspected without any knowledge of the clinical findings so that an unbiased opinion could be taken of each chest film.

All 10 new cases at Factory B and eight of the 14 new cases at Factory A had proteinuria only. It has been established that the proteinuria in the new cases is identical with that described by Kekwick (1955). Spectrophotometric examination of the urinary proteins gave extinction values at 280 mμ, in the range found for proteins, providing additional evidence that they are protein in nature. Estimation of the bound carbohydrate of these proteins by the method of Sørensen and Haugaard (1933) on three samples of the proteins gave the following values, 18·2%, 22·3%, 29·5%. These figures indicate that these are mucoproteins with a high polysaccharide content and this is consistent with their reaction to sulphosalicylic acid (Kekwick, 1957).

Proteinuria is a common finding in renal disease; in chronic glomerulonephritis, pyelonephritis, or the kidney of hypertension the proteins are plasma proteins with an excess of albumin. The protein in the urine of men suffering from cadmium poisoning is a specific protein which has a molecular weight of 20,000 to 30,000. It is not clear therefore whether this protein is present in the urine as the result of renal damage or whether it has a sufficiently small molecule to pass through a normal kidney. Since, however, this proteinuria only occurs following absorption of cadmium it is evident that a toxic process has occurred. The only other naturally occurring disease in which a specific proteinuria occurs is multiple myeloma, when Bence-Jones protein is present in the urine of a certain proportion of cases. Patients suffering from multiple myeloma can die as the result of renal failure, the histological lesion being essentially one of primary tubular damage.

Clarkson and Kench (1956) studied the amino-acid content of the urine of men exposed to lead, mercury, uranium, and cadmium, the latter as cadmium oxide dust in the accumulator industry. They found that the cadmium and uranium workers had an increased amount of amino-acids in the urine and that this finding was more marked in the cadmium workers than in those exposed to uranium. It was particularly marked in those men who were excreting the specific cadmium protein. Amino-aciduria occurring in the absence of advanced hepatic failure is a manifestation of renal tubular damage, provided the plasma amino-acid levels are not increased. The plasma amino-acid levels in workers exposed to cadmium showing the aminoaciduria are not available.

During the survey described in this paper it was found that, using a sensitive qualitative test for glucose 19 of the 82 men had glycosuria. One of these had suffered from diabetes mellitus for many years; of the remaining 18 men, 17 were also excreting the cadmium protein in the urine. This observation has been confirmed independently by Kench and Smith (1957) during routine testing of the urine of workers exposed to cadmium oxide dust in the alkaline accumulator industry. These two findings are compatible with early renal tubular damage.

Of the cases studied in hospital, one man died in uraemia from chronic renal failure (Case A1, Bonnell, 1955) and granular contracted kidneys were found at necropsy. The histological changes were non-specific but in cases of advanced renal disease it is frequently impossible to find histological evidence incriminating any one aetiological factor. Abnormal renal function tests have been demonstrated in three other cases (A2, B1, and B6, Bonnell, 1955).

Severe renal damage can be produced in rats following repeated administration of small quantities of cadmium for periods of up to one year (Bonnell, King, and Ross, in preparation). The lesion is primarily one of tubular damage, the glomeruli remaining intact. In these experiments it was shown that if the administration of cadmium was stopped after four to five months, when only a slight degree of renal damage had been produced, the kidneys of these animals were as severely affected at the conclusion of the experiment as those of the animals which had received the cadmium for 12 months. Tubular necrosis has also been produced in rabbits by Dalhamn and Friberg (1957) after daily subcutaneous injections of cadmium for 10 weeks. Knowledge will not be complete until further human cases have been studied at necropsy, but the evidence available at present suggests that progressive renal damage does occur following prolonged absorption of cadmium.

There is some evidence that the urinary excretion of cadmium may be affected by the general health of the patient. In one instance (Case B6) the cadmium content in the urine rose from 24 μg. per day to 440 μg. per day coinciding with an acute illness, in this case a spontaneous pneumothorax. In another case (A2) cadmium excretion reached a figure of 900 μg. per day during acute bronchopneumonia but when last examined this patient was excreting 25 μg. cadmium per litre of urine. Case B3 when seen in 1953 was excreting 1·24 mg. of cadmium per day in the urine. At post-mortem examination on this patient (Smith, Kench, and Smith, 1957) the bile contained 24 μg. of cadmium per g. representing an excretion of about 19 mg. of cadmium per day. The liver contained 160 μg. of cadmium per g. and at this rate of excretion all the cadmium would have been removed from the liver in three to four months. High concentrations of cadmium were also present in the aorta and main vessels in this case. This man died of acute bronchopneumonia and it could well be that cadmium was released from the tissues during this acute illness.

The analysis of the cadmium concentration of the atmosphere in both factories suggested that provided individual workmen took great care, there was probably little hazard at that time. Despite this, the measurement of cadmium on face masks worn for a single operation by men employed at Factory B showed that even under those conditions large amounts of cadmium could have been absorbed by a careless workman and suggested that the ventilation system could be improved further.

Of the 100 men first examined in 1953 at these two factories, 43 are now known to have symptoms or signs of the disease. In addition, seven other cases

are known among ex-employees. The disease is chronic and in the majority of cases patients may succumb to anoxia due to emphysema or to some intercurrent pulmonary infection before the renal lesion has had time to develop. The new cases described in this paper have in many instances no evidence of pulmonary involvement, so that in them the renal lesion may become the more important feature of the disease.

We are indebted to the medical and personnel departments of the two factories concerned for their continued assistance and wholehearted cooperation; to Dr. Donald Hunter and Dr. P. L. Bidstrup for their advice and encouragement; to Dr. R. A. Kekwick for advice and assistance in protein identification; to Dr. Richard Doll for his advice on the planning of the survey; and to Miss J. Peal and Mr. B. Biles for technical assistance. We should also like to thank Dr. E. H. Evison for consultations over Cases D1 and D2, and Dr. G. L. Manson who arranged for glucose tolerance tests in Cases B3 and B4 and renal function tests in Case B6.

REFERENCES

Armitage, P. (1955). Personal communication.
Bernstein, L., D'Silva, J. L., and Mendel, D. (1952). *Thorax*, **7**, 255.
Bonnell, J. A. (1955). *Brit. J. industr. Med.*, **12**, 181.
——, King, E., and Ross, J. H. In preparation.
Clarkson, T. W., and Kench, J. E. (1956). *Biochem. J.*, **62**, 361.
Dalhamn, T., and Friberg, L. (1957). *Acta. path microbiol. scand.*, **40**, 475.
D'Silva, J. L., Freeland, D. E., and Kazantzis, G. (1953). *Thorax*, **8**, 303.
——, and Kazantzis, G. (1954). *Ibid.*, **9**, 128.
Friberg, L. (1950). *Acta med. scand.*, Suppl. 240.
Gandevia, B., and Hugh-Jones, P. (1957). *Thorax*, **12**, 290.
Kazantzis, G. (1956). *Brit. J. industr. Med.*, **13**, 30.
Kekwick, R. A. (1955). *Ibid.*, **12**, 196.
—— (1957). Personal communication.
Kench, J. E. and Smith, J. C. (1957). Personal communication.
King, E. (1955). *Brit. J. industr. Med.*, **12**, 198.
Smith, J. C., and Kench, J. E. (1957). *Ibid.*, **14**, 240.
——, ——, and Smith, J. P. (1957). *Ibid.*, **14**, 246.
Sørensen, M., and Haugaard, G. (1933). *C.R. Lab. Carlsberg*, **19**, No. 12.
Wright, B. M. (1954). *Brit. J. industr. Med.*, **11**, 284.

APPENDIX 1

Follow-up Notes of Cases Previously Reported

Factory A.—The following cases were investigated from Factory A.

Case A5.—A man, aged 62, had cast copper-cadmium alloys from 1938 to 1950. He continued to work in the casting shop until March, 1954, when he was forced to retire because of the severity of his symptoms. He was extremely short of breath, but complained of no cough and little sputum; on clinical examination there was evidence of severe emphysema with bronchospasm. The blood pressure was 160/110 mm. Hg and the urine contained protein. The respiratory function tests were grossly abnormal (Table 8).

Case A7.—A man, aged 60, had continued to work in the casting shop but had not actually cast copper-cadmium alloys since August, 1956. He was symptom-free; on clinical examination blood pressure was 120/80 mm. Hg, no emphysema was demonstrable, but the liver was enlarged and palpable three fingerbreadths below the right costal margin. The urine contained the characteristic protein and traces of cadmium (10 to 15 μg. per litre). Glycosuria was demonstrable. Respiratory function tests showed no deterioration since 1953 and the chest radiograph was normal.

Case A8.—A man, aged 59, had cast copper-cadmium alloys from 1921 to 1943 and since that time he had worked on the manufacture of copper wire. His symptoms were more severe and he was constantly short of breath aggravated each winter by cough and sputum. On clinical examination there was evidence of severe emphysema, blood pressure was 130/90 mm. Hg, and the urine contained the characteristic protein. A mid-day sample of urine contained 70 μg. of cadmium per litre and the test for glucose was positive. There was radiological evidence of increased severity of the emphysema compared with 1953; the range of diaphragmatic movement was reduced and there was an increase of the reticular pattern of the lungs with bullous areas at both apices and at the right base. The respiratory function tests were grossly abnormal (Table 8).

Case A11.—A man, aged 69, had worked for 20 years in the vicinity of the copper-cadmium furnaces. In 1953 there was clinical evidence of chronic bronchitis and emphysema but respiratory function tests and a chest radiograph were normal. Proteinuria was demonstrable. In March, 1955, he had a cardiac infarction and was forced to retire from work. He was very short of breath and also suffered from a cough, sputum, and angina of effort. On clinical examination there was evidence of emphysema and chronic bronchitis but in addition there were signs of left ventricular failure with cardiac enlargement, ventricular extrasystoles, and a blood pressure of 160/100 mm. Hg with pulsus alternans. The characteristic protein was present in the urine and respiratory function tests were grossly abnormal (Table 8) confirming a diagnosis of emphysema. The urine contained 10 μg. of cadmium per litre.

Case A12.—A man, aged 58, had worked in the vicinity of the copper-cadmium furnaces from 1935 to 1945. He had retired from work in 1953 because of the severity of his symptoms. He complained of severe shortness of breath with "tightness" of the chest but no cough or sputum. There was clinical evidence of severe emphysema with bronchospasm, and the urine contained the characteristic protein but no cadmium was detected. The respiratory function tests (Table 8) confirmed deterioration.

Factory B.—The following cases were seen at Factory B.

Case B1.—A man, aged 56, had cast copper-cadmium alloy from 1930 to 1950. In December 1956, he complained of a sudden severe pain over the left lower part

of the chest which was accompanied by extreme dyspnoea. He had been extremely dyspnoeic since that time. On clinical examination there was evidence of advanced emphysema with bullae at both lung bases. The chest radiograph confirmed this. It is probable that he suffered a spontaneous pneumothorax in December, 1956. The respiratory function tests were grossly abnormal (Table 8). Protein was present in the urine, which also contained 25 μg. of cadmium per litre.

Case B2.—A man, aged 53, had continued to supervise the casting shop. He complained of dyspnoea on effort and winter cough; emphysema was demonstrable clinically and radiologically and the respiratory function tests were abnormal (Table 8). Proteinuria and glycosuria were demonstrated. Glucose tolerance tests showed the typical response of mild diabetes mellitus. He was excreting 20 μg. of cadmium per litre of urine.

Case B4.—A man, aged 61, had not been exposed to cadmium after 1953. Dyspnoea was more severe than at the time of the previous examination; a marked degree of emphysema accompanied by bronchospasm was evident on clinical examination. The respiratory function tests confirmed the clinical impression of deterioration (Table 8). Proteinuria and glycosuria were demonstrated. On further investigation he was shown to have a diabetic glucose tolerance curve. No cadmium was detected in the urine.

Case B5.—A man, aged 63, had not been exposed to cadmium after 1947. Shortness of breath was as severe as at the first examination, but he had not complained of cough. The chest radiograph and respiratory function tests confirmed the diagnosis of emphysema and the respiratory function tests (Table 8) showed that the emphysema was more severe. Proteinuria was present and also traces of cadmium in the urine.

Case B6.—A man, aged 54, was exposed to cadmium for seven years from 1945 to 1952. On examination in 1953 he was found to have emphysema and bronchospasm; the liver and spleen were palpable on examination of the abdomen. He remained reasonably well until August, 1956, when he was admitted to hospital because of a sudden exacerbation of dyspnoea accompanied by severe chest pain. On admission he was found to have a left-sided pneumothorax with collapse of approximately 30% of the lung. He made an uneventful recovery with symptomatic treatment. No protein was demonstrable in the urine but excretion and concentration tests of the urine showed slight impairment of renal function. On examination respiratory function tests showed marked deterioration in four years (Table 8). The chest radiograph showed an increase in size of the hilar vessels and of the transverse diameter of the heart compared with the film taken in 1953.

The daily urinary excretion of cadmium in this man was 24 μg. in 1953. During his illness in August and September, 1956, this figure rose to 440 μg. During convalescence at home, but before returning to work, the daily excretion was 153 μg. In June, 1957, by which time he had completely recovered from the acute effects of the pneumothorax and was back at work, the daily excretion was again low, namely 34 μg. of cadmium per day.

Case B7.—A man, aged 41, was symptom-free, but proteinuria and glycosuria were present on testing repeated samples of urine. The urine contained no cadmium.

Case B8.—A man, aged 40, complained of some dyspnoea on exertion but no abnormality was detected on examination. Proteinuria was again marked and glycosuria was also demonstrable. No cadmium was detected in the urine.

Case B9.—A man, aged 65, no longer worked in the casting shop and was semi-retired. He was symptom-free but proteinuria and glycosuria were present in repeated specimens of urine, which also contained 25 μg. of cadmium per litre.

Case B10.—A man, aged 45, complained of some dyspnoea on effort, but no emphysema was demonstrable on examination. Proteinuria was demonstrated but no glycosuria. The urine contained 24 μg. of cadmium per litre.

New Cases.—These cases have been seen since the report of the previous investigation.

Case D1.—A man, aged 51 years, in whom a diagnosis of emphysema with bronchospasm was made. The characteristic protein was present in the urine. He had worked from 1933 to 1939 casting copper-cadmium alloys at Factory A. He served in the armed forces from 1939 to 1942 when he was discharged to carry out essential industrial work; he continued casting copper-cadmium alloys from 1942 to 1945. Since 1945 he had worked as a bus conductor.

He was quite well until 1945 when he first became short of breath on exertion with "tightness" of the chest and a slight unproductive cough. The dyspnoea gradually increased in severity and had become severe since 1951 following an acute attack of bronchitis. Dyspnoea had been constant since 1954.

On examination in May, 1957, there was a slight degree of cyanosis but no finger clubbing. The chest was fixed in inspiration. There was complete absence of cardiac and liver dullness on percussion and the heart sounds were best heard over the xiphisternum. The chest was hyperresonant on percussion, breath sounds were vesicular, and many high-pitched rhonchi were heard. The urine contained the characteristic protein and 12 μg. of cadmium per litre.

Case D2.—This was a man aged 63 years who had proteinuria only. He had worked from 1939 to 1956 in the casting shop at Factory A casting brass, bronze, and copper-cadmium alloys. He had refused to take part in the survey in 1953, but did provide an early morning specimen of urine which at that time was normal.

For 12 months he had complained of dyspnoea on exertion with cough and sputum for nine to 10 months. On examination in May, 1957, he was not cyanosed and the fingers were not clubbed. Chest expansion was 1½ inches. Cardiac and liver dullness were within normal limits on percussion of the chest. The breath sounds were vesicular, air entry was good at both the apices and bases of the lungs, and occasional rhonchi, dispersed by coughing, were heard. There was no evidence of emphysema.

The characteristic protein was present in the urine, which contained 10 μg. of cadmium per litre.

APPENDIX 2

Dust respirators should not be used as the primary protection against dusts or fume, but only as additional safeguards when the nature of the work does not allow adequate exhaust ventilation covering the source of emission at all times. During the manufacture of copper-cadmium alloys the workmen are required to be close to the source of cadmium oxide fume and respirator protection at these times would reduce their exposure to the fume.

The effective use of respirators requires that they should be efficient against the type of material concerned; that they should be sufficiently comfortable under conditions of temperature and exertion so as not to reduce the efficiency of the workmen; and that supervision is available to ensure their use at the appropriate times. These conditions appeared to be satisfied in Factory B by the Siebe Gorman "microfilter" dust respirators. In order to obtain data on their efficiency in the working conditions observed against cadmium oxide fume two respirators were obtained after their use by two workmen during a series of mixing and casting operations.

The wadding filters of the respirators were each divided into six approximately equal sections from front to rear of the mask, and analysis for cadmium content was performed on each section. In order to avoid errors arising from sparks trapped in the first sections, the data plotted in Fig. 3 give the amount in any one section of each mask as a percentage of the total amount in that section and those to the rear of it. Thus the higher apparent efficiencies of the first two sections were possibly caused by the presence of large particles, but the next three each showed an efficiency of about 50% which may be assumed to be against the residual fume after the removal of particles formed by sparks.

The data obtained thus showed that each section of the filters contained about 50% of the cadmium oxide fume entering it. The overall efficiency is therefore that of six sections in series, each of 50% efficiency, to give a very high overall efficiency. These respirators can therefore be accepted as suitable protective devices to be used in addition to exhaust ventilation covering the sources of the cadmium oxide fume.

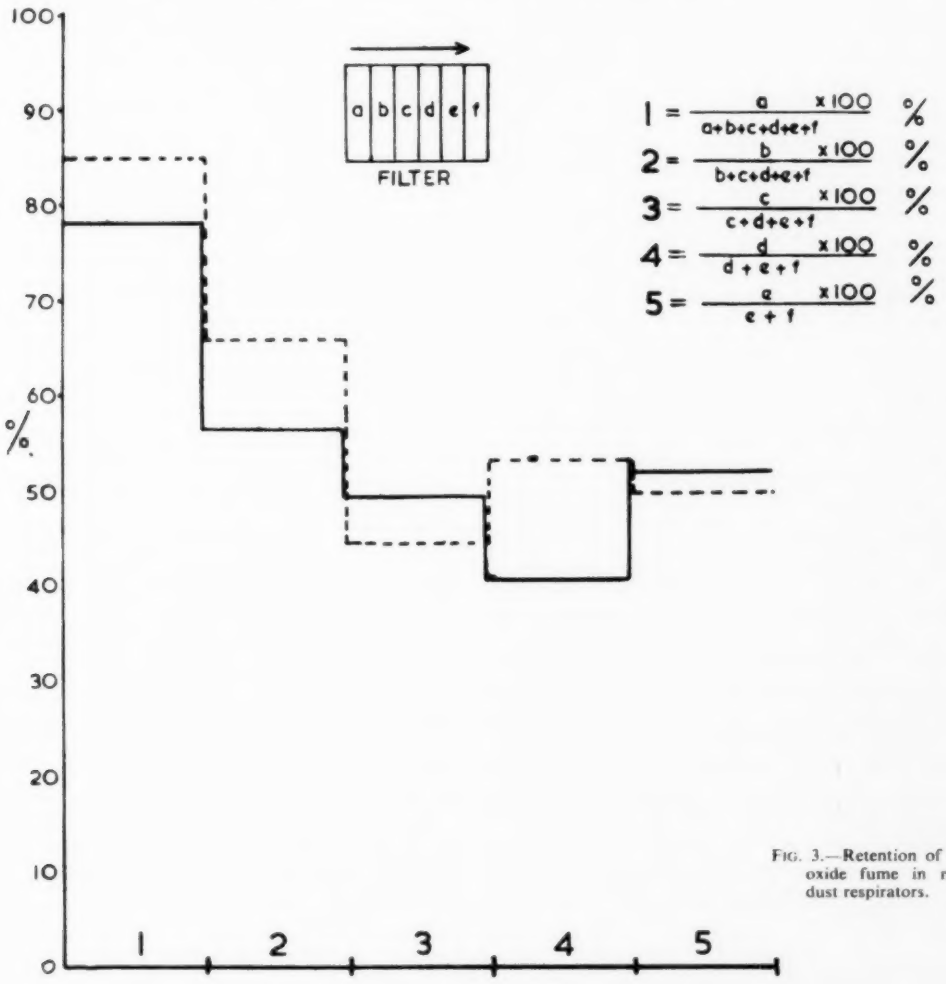


FIG. 3.—Retention of cadmium oxide fume in microfilter dust respirators.

Brit. J. industr. Med., 1959, **16**, 148.

THE VALUE OF MOBILIZATION OF LEAD BY CALCIUM ETHYLENE-DIAMINE-TETRA-ACETATE IN THE DIAGNOSIS OF LEAD POISONING

BY

J. TEISINGER and J. SRBOVÁ

From the Clinic for Occupational Diseases, Prague, and the Institute of Industrial Hygiene and Occupational Diseases, Prague

(RECEIVED FOR PUBLICATION JULY 23, 1958)

Traditional laboratory tests for lead poisoning tend to fail in cases where a considerable interval has elapsed since exposure. We have used calcium ethylene-diamine-tetra-acetate ($CaNa_2EDTA$) for the quantitative mobilization of lead for diagnostic purposes.

In a control group of 50 individuals who had never worked with lead it was found that the average urinary excretion of lead in 24 hours amounted to 0·031 to 0·043 mg. The maximum value did not exceed 0·100 mg. After intravenous injection of $CaNa_2EDTA$ the amount of excreted lead rose considerably, but did not exceed 0·350 mg./24 hr.

In a group of 47 individuals who had formerly worked with lead or who were still engaged in this work but did not show any symptoms of poisoning, the urinary lead levels before injection were higher than in the control group. After injection of $CaNa_2EDTA$ the lead excretion in 24 hours increased considerably. After injection of $CaNa_2EDTA$, patients suffering from chronic lead poisoning showed a considerable increase of urinary lead excretion, which attained the order of milligrams in 24 hours.

The fractionated examination of the urine of 10 unexposed individuals, undertaken at intervals of three hours, showed after injection of $CaNa_2EDTA$ no higher lead concentration than 0·500 mg./litre, the highest concentrations being observed six hours after injection. In the urine of individuals exposed to lead or suffering from lead poisoning a higher urinary lead concentration was found than in the control group, and the maximum was in these cases found at various time intervals.

It is concluded that the mobilization of lead may be of considerable value in the diagnosis of atypical cases of chronic lead poisoning, but the results can be evaluated only in association with the general clinical picture.

The laboratory tests at present employed for the diagnosis of lead poisoning have proved satisfactory. They fail, however, in cases where exposure is not very severe and particularly when a considerable time has elapsed since termination of exposure. In such cases it may then be difficult to decide whether the symptoms and signs are due to lead poisoning. Traditional procedures, such as the administration of sodium bicarbonate, potassium iodide, parathormon, and vitamin D, to mobilize lead supplies in the human body and to increase urinary excretion have given poor results. We have found that $CaNa_2EDTA$ is excreted more rapidly than PbEDTA. Experience in treating patients with chronic lead poisoning by means of $CaNa_2EDTA$ has shown this preparation to give much better results than the older methods. Several authors have considered the problem of how to effect the quantitative mobilization of lead for diagnostic purposes by means of this preparation (Rieders and Brieger, 1955; Teisinger and Srbová, 1956; Desoille, Albahary, Truhaut, and Boudene, 1957; Bastenier, Deslypere, and Mme. de Graef-Millet, 1957; Zahorski and Myslak, 1957). The work described in the present paper was undertaken to measure the urinary lead excretion after administering $CaNa_2EDTA$ to normal and lead-exposed subjects, and to attempt to relate the amount of urinary lead excreted to the diagnosis of lead poisoning.

TABLE I

URINARY LEAD EXCRETION (MG.) IN 24 HOURS

Group	No. of Cases		Before Injection of $CaNa_2$ EDTA	After Injection of $CaNa_2$ EDTA
Normal	50	99% confidence limits of average value	$0.031 < \bar{x} < 0.043$	$0.143 < \bar{x} < 0.153$
		Extreme values	0·016 — 0·099	0·058 — 0·352
Exposed	47	99% confidence limits of average value	$0.067 < \bar{x} < 0.082$	$0.612 < \bar{x} < 0.629$
		Extreme values	0·012 — 0·268	0·166 — 3·212

Method

Two groups of in-patients at the Prague Clinic for Occupational Diseases were selected for the investigation. The first group of 50 patients had never been exposed to lead; the second group of 47 patients had worked with lead in various occupations (manufacture of lead paint, storage batteries, enamels, smelting, type casting). Each patient was given a single intravenous injection of 15 ml. of a 20% solution of calcium disodium ethylene-diamine-tetra-acetate (2·8 g. of anhydrous substance). The Czechoslovak preparation "edtacal, Spofa" was used as it had previously given good results. Urine was collected for 24 hours, for one to two days before injection and on the day after injection. The urinary lead content was determined by the method of Srbová and Teisinger (1957), in which the lead is precipitated as phosphate, dissolved in hydrochloric acid, and determined polarographically.

Results

The results are given in Table 1.

In both groups lead excretion was significantly increased following injection of $CaNa_2EDTA$.

On the day after injection the urinary lead was also significantly increased compared with that of the day before injection, but did not attain such high values. In the group of 50 people not exposed to lead the urinary lead did not exceed 0·100 mg./24 hr. before injection and 0·350 mg./24 hr. after injection of $CaNa_2EDTA$.

Most of those exposed to lead had discontinued work with lead for several months—in some cases several years; only eight were still engaged in this work. Some of these cases had been sent to the clinic for investigation as it was known that they had worked with lead; others were suffering from unrelated illnesses. None of these patients had symptoms or signs of classical lead poisoning; the usual laboratory tests gave no results indicative of lead poisoning.

It was first established whether the urinary lead in the specimen collected on the day before injection varied from the values found in the urine of the 50 unexposed individuals. On the day before injection there was in fact a significant difference between the two groups (Table 1). The average value in the exposed group was within the confidence limits of $0.067 < \bar{x} < 0.082$ mg./24 hr., with a probability of 99%, the extreme values obtained being 0·012 and 0·268 mg./24 hr.

The difference between the two groups was also significant on the day of injection. The average in those exposed lay with a probability of 99% within the confidence limits of $0.612 < \bar{x} < 0.629$ mg./24 hr., the extreme values being 0·166 and 3·212 mg./24 hr. On the day after injection there was also a significant difference between the two groups.

Thus it was proved that, following injection of $CaNa_2EDTA$, the average lead excretion of people working with lead rose markedly in comparison with those not exposed to lead.

Thirty-five individuals of the group exposed to lead were then examined by laboratory tests; stippled erythrocyte counts, blood lead, and urinary porphyrins were determined. In 28 cases lead mobilization by $CaNa_2EDTA$ was positive; in the remaining seven cases lead mobilization was negative as the urinary lead values were below the limit of 0·350 mg./24 hr. In the group with positive lead mobilization urinary lead values varied from 0·415 to 3·21 mg./24 hr. Stippled erythrocytes exceeding 1,000 per million red cells were present in 50% of these cases; plumbaemia above 0·070 mg. % (this is the normal upper limit according to our polarographic method) was found in 50%. The increased plumbaemia, however, did not always correspond to an elevated lead level in the urine. The number of cases with increased porphyrinuria (the normal upper limit was considered to be 0·160 mg./24 hr.) was least, *i.e.*, only 16 %. No relation between the results of laboratory tests and the mobilization of lead by $CaNa_2EDTA$ was therefore found. Most of these individuals had discontinued working with lead some months or years previously (nine of them had experienced clinical lead poisoning some years ago). This group, however, included two extreme cases of type casters who had discontinued working with lead 15 and 19 years previously, and, on injection of $CaNa_2EDTA$, excreted 0·415 mg. and 0·533 mg. respectively of urinary lead in 24 hours. Of the seven cases in which the lead mobilization by $CaNa_2EDTA$ was negative five were employees at a printing works. Four of these showed an increased number of stippled erythrocytes, from 1,700 to

3,100 per million red cells; blood lead and urinary porphyrins were within normal limits.

The group of 47 lead-exposed individuals were suffering from various conditions; eight had symptoms of arteriosclerosis, 12 had affections of the lung such as silicosis (including lead-miners), emphysema of the lung, and tuberculosis; others were suffering from neurosis and diseases of the liver. Only two cases were suffering from chronic lead poisoning. In several cases of patchy disseminated lesions of the central nervous system and in two cases of polyneuritis a connexion with lead poisoning was suspected. In all cases of arteriosclerosis, which was found in older patients only, we rejected a connexion with lead poisoning despite a positive result for mobilization.

Patients Suffering from Chronic Lead Poisoning

In recent years, more than 120 patients suffering from chronic lead poisoning have been treated at the Occupational Diseases Clinic by means of $CaNa_2EDTA$. In all cases a considerable amount of lead was excreted on the day of injection. In order to determine whether there is any relation between the degree of poisoning and the amount of lead excreted after the first injection, we selected at random 10 cases of more serious lead poisoning (as evidenced by anaemia, colic, severe subjective symptoms, and high values in laboratory tests) and 10 slight cases showing a fall in haemoglobin. The laboratory tests (stippled erythrocyte count, blood lead, and urinary porphyrins) gave positive results in all 20 cases. It was found that lead excretion was considerably increased in the severer cases, amounting to values from 6·2 to 15·2 mg./24 hr. In two cases, however, lead excretion attained only 1·36 and 1·74 mg., although clinically these two cases were as severe as the others.

In the group of slight or "laboratory" poisoning the urinary lead values varied around 2·5 mg./24 hr., but in two cases values as high as 7·32 and 8·92 mg. were found. These two individuals had no symptoms but all laboratory tests were definitely positive.

The degree of severity of lead poisoning seems therefore to be proportional to the urinary lead level after injection of $CaNa_2EDTA$. This rule, however, is not without exception, and a mere evaluation of the result of the first injection alone is not sufficient to estimate the severity of the lead poisoning.

Lead Concentration Found by Fractionated Investigation of Urine

In all the above cases the absolute amount of urine excreted in 24 hours was determined, which was practicable as all the individuals were detained in hospital. This method is not suitable for out-patients as it is difficult to obtain the full amount of urine excreted in 24 hours. We therefore collected the urine from some further patients, three, six, nine, 12, and 24 hours after injection, determined the lead content and calculated the concentration per litre. The same dose of $CaNa_2EDTA$, 3 g., was injected intravenously as in the above cases. Some of the patients were given one litre of weak tea before injection.

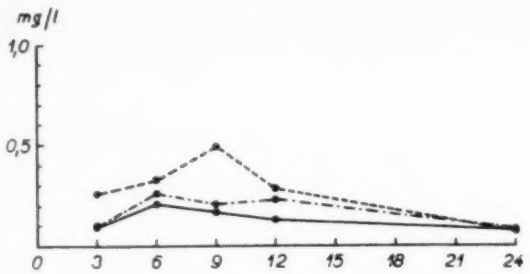


FIG. 1.—Lead concentration in the urine of unexposed individuals after intravenous injection of 3 g. of $CaNa_2EDTA$.

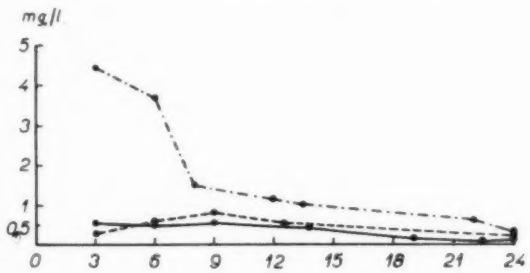


FIG. 2.—Lead concentration in the urine of individuals previously exposed to lead after intravenous injection of 3 g. of $CaNa_2EDTA$.

In 10 individuals who had never been exposed to lead and had normal liver function tests, the lead concentration in none of the specimens exceeded 0·500 mg./litre. The maximum concentration was usually found six hours after injection, sometimes after nine hours (Fig. 1).

In four individuals who did not show any symptoms of lead poisoning but had formerly worked with lead, concentrations of 0·500 mg./litre and higher, up to 4·5 mg./litre, were found. The maximum concentrations were found at various time intervals (Fig. 2). In view of the small number of cases it was not possible to evaluate the relation between the amount of lead determined and the time elapsed since the termination of exposure, nor the severity of the hazard.

In seven patients with typical symptoms of chronic lead poisoning, higher urinary lead concentrations were found, irrespective of whether tea was given

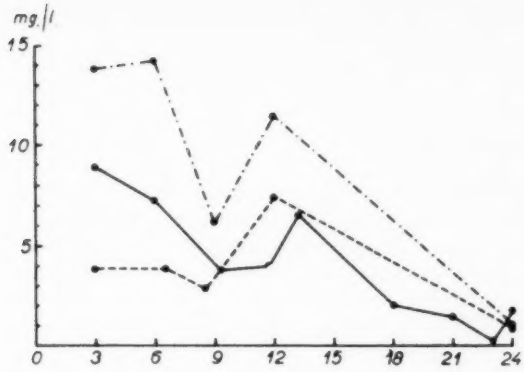


FIG. 3.—Lead concentration in the urine of patients suffering from chronic lead poisoning after intravenous injection of 3 g. of $CaNa_2EDTA$.

before injection or not (three patients received tea and four did not). The maximum concentrations were found at differing time intervals, the highest value amounting to 21 mg./litre after six hours (without tea). In these cases the time of urine sampling was evidently of no importance, as all values were much above the normal limits (Fig. 3).

Discussion

The published data relating to normal lead content in human urine show considerable differences. In the U.S.A. a lead content of 0·01 to 0·08 mg./litre is considered normal (Kehoe, 1949). The Commission for Lead Poisoning of the American Public Health Association stipulated in 1943 that a lead excretion exceeding 0·150 mg./litre of urine indicated exposure to lead (Waldman and Seideman, 1950). In the U.S.S.R. values exceeding 0·06 mg./litre are considered as indicating slight poisoning (Lazarev, 1954). In our opinion these differences are partly due to the use of different analytical techniques but there is also a real difference. Different living conditions, food supplies, different lead content in soil and vegetables, must be taken into consideration. Based upon our previous experience and the results given in this paper, we consider that in Czechoslovakia an amount of 0.100 mg. of lead in 24-hour urine is to be considered the highest normal value. On an average, however, the values are much lower, *i.e.*, 0·031 to 0·043 mg./24 hr.

In the literature we could find few references to the absolute amount of lead excreted in 24 hours by normal individuals after injection of $CaNa_2EDTA$. Hardy, Elkins, Ruotolo, Quinby, and Baker (1954) found in three control individuals after intravenous infusion an increase from 0·09 to 0·65 mg./24 hr. and less. Rieders and Brieger (1955) report that after intravenous infusion an amount of 1 mg. of lead/litre of urine (from a 24-hour sample) indicates increased deposition of lead in the body. A similar result, after intravenous infusion of 2 g. $CaNa_2EDTA$, was obtained by Desoille *et al.* (1957), who gave a value of 0·8 to 1 mg. per litre of urine as indicating a positive result in this new test, although the amounts found in their three control cases did not exceed a concentration of 0·530 mg./litre. These limit values seem high, but it is difficult to compare our results as different doses of $CaNa_2EDTA$ were given. We have previously attempted to show (Teisinger and Srbová, 1956) that intravenous infusion gives somewhat better results than intravenous injection, which, however, is better suited to current practice. An intravenous injection of 1 g. of $CaNa_2EDTA$ was given by Salvini (1955) who concluded that normal individuals excrete up to 0·5 mg. of lead in 24 hours. In our opinion, after intravenous injection of $CaNa_2EDTA$, urinary excretion of lead in unexposed individuals does not exceed 0·350 mg./24 hr. A dose of 3 g. $CaNa_2EDTA$ was chosen because we had obtained satisfactory experience with this amount in the treatment of lead poisoning as well as for diagnostic purposes, but the possibility of a reduction of this dose is not excluded. It would, however, be necessary to re-examine the limit values if the dose were reduced. The method employed by us is, of course, intended for patients in hospital.

Bastenier *et al.* (1957) suggested a method suitable for out-patients. They administered 12 mg. per kg. body weight of $CaNa_2EDTA$ and determined the lead content in the urine three and six hours later. In 20 unexposed individuals the lead concentration in the urine after three hours did not exceed 0·300 mg./litre. In our group of 50 people we observed a maximum concentration of 0·390 mg./litre, but the apparent agreement between these two figures is probably fortuitous, because we determined the total concentration in the urine after 24 hours and administered larger doses. In 10 further unexposed individuals we observed concentrations up to about 0·500 mg./litre not less than six hours after injection. This result was probably due to the larger dose of $CaNa_2EDTA$ than that given by Bastenier *et al.* It is of little importance whether the limit value is given as 0·300 mg./litre or 0·500 mg./litre as the small lead deposits thus revealed are not likely to be of clinical significance. As the urinary lead concentration depends to a large extent on diuresis, it might be advantageous to give one litre of tea to the fasting patient,

Oral administration of $CaNa_2EDTA$ has also been employed for diagnostic purposes. Desoille *et al.* (1957) administered 4 g. in two portions and gave

an upper limit in unexposed persons of 0·500 mg./litre. They found that the level of urinary lead was not so high as after intravenous administration. $CaNa_2EDTA$ is only slightly absorbed by the alimentary tract; Foreman and Trujillo (1954) found 4·2 ± 2% absorbed, White (1953) found 1·5 – 4·5%, while we found an average of 2·6% to be absorbed (Srbová and Teisinger, 1957).

The significance of diagnostic mobilization of lead may be considerable in cases in which latent saturnism is suspected, particularly in patients whose exposure to lead ceased some months or years ago. In such cases, diagnostic mobilization of lead may be a valuable aid to diagnosis: confirmation of the diagnosis is given by successful deleading treatment with $CaNa_2EDTA$.

In manifest cases of chronic lead poisoning diagnostic mobilization of lead is unnecessary. The clinical picture and laboratory tests are sufficient. Lead mobilization is of importance in deciding the method of treatment. We agree with Bastenier *et al.* (1957) that mobilization is useful for the control of deleading treatment.

The magnitude of the lead deposit which manifests itself by increased excretion after injection of $CaNa_2EDTA$ is related to the severity of the clinical picture, but exceptions corresponding to individual susceptibility are encountered. The magnitude of the lead deposit in the human organism required to cause positive laboratory tests or definite symptoms of poisoning is not known. There is at present no method available for determination of this critical magnitude. In treatment by means of complex-forming substances the lead is flushed out mainly from the parenchymatic organs. The effect of $CaNa_2EDTA$ probably consists of speeding the spontaneous transference of the Pb^{++}ions from cells into intercellular fluid by a disturbance in the equilibrium of this system. A direct effect on lead bonds in the cells appears less likely (Teisinger, Zumanová, and Žežula, 1958; Teisinger, Luštinec, and Srbová, 1958).

The question whether diagnostic mobilization of lead is of greater significance for the hygienist than biological tests cannot at present be answered as among our patients there were only a few who worked regularly with lead up to the time of examination.

The preparation BAL (2:3 dimercapto-propanol) has also been used for diagnostic mobilization of lead. Vigliani and Zurlo (1951) investigated urinary lead excretion following injection of BAL, and observed a considerable increase, especially in the first few hours after injection. The total amount excreted in 24 hours was on average 2·6 times that excreted before injection. Comparison of the values given by Vigliani and Zurlo in severer cases of lead poisoning with our results obtained after injection of $CaNa_2EDTA$ in cases of approximately the same nature showed BAL to be less efficient. Preda, Dinischiotu, Pilat, and Ionescu (1957) also observed mobilization of lead with increased excretion after injection of BAL. They concluded that the urinary lead concentration three hours after injection indicated the degree of the mobilizing effect. Their results also confirm our opinion that BAL is less effective than $CaNa_2EDTA$ in increasing the urinary lead excretion.

We are greatly indebted to Mg. Mat. Soňa Drdková for the statistical work.

References

Bastenier, H., Deslypere, P., and Mme. de Graef-Millet (1957). Proc. 12th Internat. Congr. Occup. Hth. Vol. III, p. 243. Helsinki 1st-6th July, 1957.
Desoille, H., Albahary, C., Truhaut, R., and Boudene, C. (1957). *Ibid.*, p. 287.
Foreman, H., and Trujillo, T. (1954). *J. Lab. Clin. Med.*, **43**, 566.
Hardy, H. L., Elkins, H. B., Ruotolo, B. P. W., Quinby, J., and Baker, W. H. (1954). *J. Amer. med. Ass.*, **154**, 1171.
Kehoe, R. A. (1949). In *Industrial Hygiene and Toxicology*, ed. F. A. Patty, Vol. II, p. 662. Interscience Publishers, New York.
Lazarev, N. V. (1954). *Vrednyje Vechestva v Promyshlennosti*, Part II, Leningrad 1954, p. 440.
Preda, N., Dinischiotu, G. T., Pilat, L., and Ionescu, C. (1957). *Arch. Mal. prof.*, **18**, 145.
Rieders, F., and Brieger, H. (1955). Proc. 7th Annual Meeting of the American Academy of Occupational Medicine, Philadelphia, February 10th-12th, 1955.
Salvini, E. (1955). *Folia med. (Napoli)*, **38**, 168.
Srbová, J., and Teisinger, J. (1957). *Arch. Gewerbepath. Gewerbehyg.*, **15**, 572.
Teisinger, J., Luštinec, K., and Srbová, J. (1958). *A.M.A. Arch. industr. Hlth.* **17**, 302.
——, and Srbová, J. (1956). *Arch. Gewerbepath. Gewerbehyg.*, **14**, 579.
——, Zumanová, R., and Žežula, I. (1958). *A.M.A. Arch. industr. Hlth.*, **17**, 295.
Vigliani, E. C., and Zurlo, N. (1951). *Brit. J. industr. Med.*, **8**, 218.
Waldman, R. K., and Seideman, R. M. (1950). *Arch. industr. Hyg.*, **1**, 290.
White, C. (1953). Cited by G. Maison (1953). *A.M.A. Arch. industr. Hyg.*, **7**, 145.
Zahorski, W., and Myślak, Z. (1957). Proc. 12th Internat. Congr. Occup. Hth. Vol. III, p. 242. Helsinki 1st-6th July, 1957.

Brit. J. industr. Med., 1959, **16**, 153.

THE MECHANICAL PROPERTIES OF THE LUNG IN PNEUMOCONIOSIS OF COAL-MINERS*

BY

G. L. LEATHART

From the Nuffield Department of Industrial Health, King's College, Newcastle upon Tyne, University of Durham

(RECEIVED FOR PUBLICATION SEPTEMBER 1, 1958)

To assess changes in the mechanical properties of the lungs in pneumoconiosis, the "elastance" (coefficient of elastic resistance, the reciprocal of compliance) of the lung and resistance of the airways were measured by the method of Mead and Whittenberger (1953) in 97 coal-miners and 17 men who had never worked underground. Ages ranged from 24 to 57. The work done on the lung was measured in 66 of these subjects, and the maximum voluntary ventilation (M.V.V.) was measured in all. The subjects were obtained by random selection from hospital out-patients and by random selection from a radiological survey of over 5,000 coal-miners. The M.V.V. was reduced in coal-miners with progressive massive fibrosis (P.M.F.), and in those without pneumoconiosis, but was not significantly reduced in simple pneumoconiosis. Elastance of the lung was unaltered in young miners but was slightly, and significantly, increased in all elderly faceworkers whatever the radiological category. This change appeared to be due to long years of work underground rather than to the radiological abnormality of pneumoconiosis. This slight change in the pulmonary elastance cannot be the cause of the reduction in M.V.V., since the two are unrelated. Inspiratory resistance was normal in all coal-miners, suggesting that pneumoconiosis is not associated with any fixed distortion of the airways. The non-elastic work of breathing, however, was frequently above normal and this suggests that bronchial obstruction develops rather commonly during expiration. This change appears to be the cause of reduction of M.V.V. in the majority of cases, as a negative correlation between M.V.V. and non-elastic work was established. Mean non-elastic work was not, however, unduly high in those radiological groups in which a significant reduction of M.V.V. was recorded. It is suggested that this discrepancy may be due to excessive frictional resistance in the chest wall of miners with P.M.F. and those with no radiological abnormality. The findings are consistent with the hypothesis that emphysema is abnormally common in elderly coal-miners, and that it, rather than pneumoconiosis, is the cause of their reduced ventilatory ability.

A great deal of work has been done to establish the cause of dyspnoea in coal-miners and its relationship to pneumoconiosis. This has been reviewed by Gilson and Hugh-Jones (1955) who themselves carried out a comprehensive series of pulmonary function tests on a group of miners and normal controls. It has been shown that there is a reduction of ventilatory capacity in coal workers with pneumoconiosis, especially when progressive massive fibrosis is present. On the other hand Carpenter, Cochrane, Gilson, and Higgins (1956) found that, in a random sample of a population, the ventilatory capacity of miners without pneumoconiosis was more severely restricted than that of miners with simple pneumoconiosis. This suggests that the dyspnoea which afflicts miners may be due to something other than simple pneumoconiosis. Moreover, Newell and Browne (1955) were unable to find any correlation between respiratory disability and simple pneumoconiosis in a large series of working miners.

There are two ways in which pneumoconiosis might reduce ventilatory capacity. The large fibrotic masses which develop in the lungs of an advanced case of pneumoconiosis undoubtedly cause compression or kinking of the bronchi in some cases, and thus increase the resistance of the airways. Obstruction of the airways can also occur without fibrosis, as in asthma. Secondly, the fibrous tissue itself probably makes the lungs stiffer than normal. Both

*The results of this investigation were presented briefly at the Twelfth International Congress on Occupational Health, Helsinki, July, 1957.

these changes would tend to lower the ventilatory capacity and to cause dyspnoea. Measurement of these two factors might help to increase our understanding of the dyspnoea of coal-miners. It should establish whether there is any significant stiffness of the lungs or obstruction of the airways in simple pneumoconiosis and should confirm that it is present in P.M.F. In particular it might offer some explanation for the low ventilatory capacity of coal-miners without pneumoconiosis.

This paper presents the results of the determination of elastance and total non-elastic resistance (sum of airway and pulmonary viscous resistance) in a series of 105 miners and 10 controls. Maximum voluntary ventilation was also measured in these subjects.

Methods

A pilot study was done on a group of hospital patients and then an older group, chosen at random from a selected mining population, was investigated.

The hospital patients were aged 24 to 48 years (mean age 39 years) and included 37 coal-miners and 10 controls who were not miners. None of the patients was in need of medical treatment at the time of investigation and they were chosen at random from the out-patient files of the Nuffield Department of Industrial Health in the University of Durham, England. None of the control cases had any respiratory symptoms, and not one of them was investigated until 18 months had elapsed since his first hospital attendance.

The majority of the control cases were people who were thought to have undergone the risk of industrial poisoning, but were found to be normal. The diagnoses are given in Table 1. The four men who had been exposed to vanadium had all changed their work two years before investigation. If this exposure had left any residual damage, of which there were neither signs nor symptoms, this would tend to decrease the differences between the subjects and the controls, rather than to exaggerate them.

TABLE 1

DIAGNOSIS OF NON-MINING CONTROLS

Age	Occupation	Diagnosis
24	Fitter—heavy engineering	Exposed to vanadium
29	Plant mechanic	Exposed to vanadium
31	Fitter—heavy engineering	Exposed to vanadium
33	Labourer—road works	Idiopathic epilepsy
34	Charge hand—rubber factory	Exposed to $CHCl:CCl_2$
35	Physician	Bornholm disease
36	Lead furnace man	No abnormality
38	Millwright	Exposed to vanadium
38	Charge hand—zirconium plant	No abnormality
39	Labourer in lead works	No abnormality

The other group, consisting of 68 coal-miners, aged 52 to 57 years (mean age 54), were selected at random from among those men of this age whose chest radiographs had been classified during a survey of four Durham coal-mines in 1950-51. The size of the sample, of the population from which it was drawn, and the number of men who actually completed the tests are shown in Table 2.

TABLE 2

SAMPLE OF COAL-MINERS (AGE 52-57)

Radiological category	0	1 + 2	3	P.M.F.
Number of men aged 52-57 years	281	194	104	23
Size of random sample	30	30	30	23
Number examined	19*	24	11	14

*One subject was excluded from part of the statistical analysis.

There was a high lapse rate. Measurement of oesophageal pressure cannot be done without the cooperation of the subject and no effort was made to compel attendance from those who were unwilling to come. Each person who failed to keep his first appointment was offered several more, but the reluctant attender often refused oesophageal intubation and nothing was gained by encouraging his attendance. Thus this work reports the results in those men who were sufficiently brave, frightened, interested, hopeful, grateful, ill, or well to attend and cooperate. It is impossible to say how this has influenced the results, but there is no reason to suppose that this influence will have been exerted more in one radiological category than another, and comparison of the mean results in different categories is probably justifiable.

Eight of these 68 miners had never worked on the coalface. They were employed as power station attendant, colliery wages clerk, washery foreman, weighman, winding-engine man, screener, horsekeeper, and wagon man. The horsekeeper had worked underground for 40 years, the others not at all. Seven cases of asbestosis aged 45 to 62 (mean age 54) were also examined. These were attending the out-patient department on account of respiratory symptoms and all had abnormal chest radiographs. These cases will be discussed in greater detail in another paper.

All subjects were examined seated. Maximum voluntary ventilation was determined using a mouthpiece, valve-box, and plastic bag; the mean of three attempts of 15 seconds' duration was recorded after one practice run. The volume was not corrected to body temperature, and the frequency of respiration was not systematically recorded.

Elastance and non-elastic resistance were calculated by the method of Mead and Whittenberger (1953). Intra-oesophageal pressure, minus pressure in the mouth, was measured with an air-filled balloon passed through the nose, and was displayed on an oscilloscope. Velocity of air flow was measured at the mouth with a wire-mesh pneumotachograph (Lilly, 1950) and tidal air with a spirometer with a light bell (Dornhorst, Semple, and Young, 1953). These were all displayed simultaneously on an oscilloscope and the resulting records were photographed. Preliminary experiments established that the oesophageal balloon and the pneumotachograph gave similar responses to a square wave input (90% response in 0·06 sec.). Simultaneous records from pneumotachograph and spirometer showed that the lag in the spirometer was never greater than 0·03 sec. at all respiratory frequencies from 15 to 70 cycles per minute.

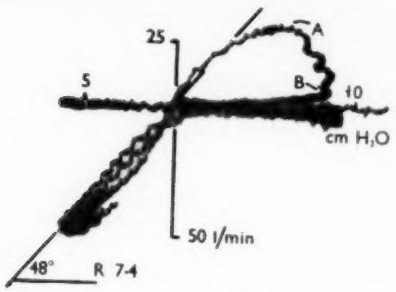


FIG. 1.—Tracing obtained by method of Mead and Whittenberger (1953). Abscissa = intra-oesophageal pressure in cm. of H_2O. Ordinate = velocity in litres per minute. Inspiration downwards. The cotangent of the angle, 48°, is proportional to the resistance. In expiration the resistance is non-linear and rises to infinity at point B.

In many subjects the non-elastic resistance alters throughout the respiratory cycle, increasing with increasing velocity of air flow and also with diminishing chest volume (Dayman, 1951). In order to get comparable figures, the resistance has been measured during inspiration only, by fitting a straight line to the record obtained at velocities of less than 60 l. min., represented by a line some 20-30 mm. long on the photographic record (Fig. 1). The resistance is proportional to the slope of this line. The non-elastic resistance was worked out from three or more breaths in each subject, and the result is the mean of these.

In the older group a pressure volume diagram for the lung during normal respiration was also photographed, and the non-elastic work of respiration was calculated from the area of the closed loop in two successive breaths (standard error ± 9% of the mean). A time base was included on the pressure volume record, so that the ventilation rate could be determined. Elastance was also determined from the pressure volume diagram and gave good agreement with the figure obtained by the method of Mead and Whittenberger (correlation coefficient = 0·885). The standard error of replicate determinations of elastance was ± 0·3 units.

The calibration of the instruments was checked during and after each test with standard pressures measured with a water manometer, standard volumes measured with a spirometer, and a standard flow rate supplied by a pump which delivered about one litre per second (confirmed, over the course of one minute, with a dry gas meter, at the end of each experiment). All volumes were measured at ambient temperature and pressure, and have not been corrected. During these investigations the subjects chose their own rate and depth of respiration. They were encouraged to breathe normally during the determination of elastance, resistance, and non-elastic work, but, in fact, the ventilation was usually rather large, ranging from 10·1 to 32 l. min. (mean 17·9 l. min.).

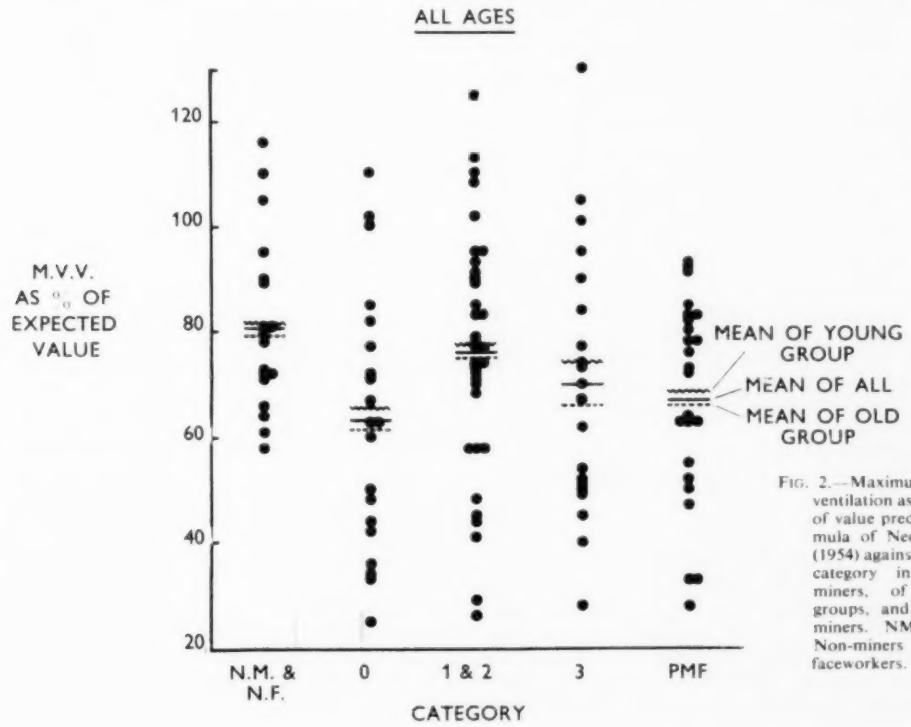


FIG. 2.—Maximum voluntary ventilation as a percentage of value predicted by formula of Needham *et al.* (1954) against radiological category in 105 coal-miners, of both age groups, and in 10 non-miners. NM and NF = Non-miners and non-faceworkers.

TABLE 3

RESULTS IN YOUNGER MEN

Radiological Category	Number	Mean Age (years)	Mean M.V.V.F (l./min.)	Mean Elastance (cm. H_2O/l.)	Mean Inspiratory Resistance (cm. H_2O/l./sec.)	Mean Dyspnoea
Non-miners	10	34	107·0	4·5	1·3	0·2
0 S.D.		4·7	23·7	1·3	0·49	0·63
Miners	9	39	80·1	4·2	2·4	0·9
S.D.		5·9	29·3	1·2	1·64	1·17
1 and 2	9	38	99·1	4·4	2·1	1·2
S.D.		2·8	28·3	1·5	1·26	1·09
3	9	40	92·1	5·7	2·0	1·4
S.D.		3·2	29·9	1·8	1·11	1·51
P.M.F.	10	43	81·4	6·4	2·3	1·8
S.D.		3·4	26·9	2·7	1·21	1·32
Significance All miners compared with non-miners			Not significant t test (45 d.f.) 2·00	Not significant t test (45 d.f.) 1·09	t test (44 d.f.) 2·21 $P < 0·05$	$\chi^2 = 5·85$* (1 d.f.) $P < 0·02$

*Based on number of men without dyspnoea.

TABLE 4

RESULTS IN OLDER MEN

Radiological Category	Number	Mean Age (years)	Mean M.V.V.F (l./min.)	Mean Elastance (cm. H_2O/l.)	Mean Inspiratory Resistance (cm. H_2O/l./sec.)	Mean Total Non-elastic Work (kg.m./l.)	Mean Ventilation Rate (l./min.)	Mean Dyspnoea
Non-faceworker	8	54	85·6	4·4	2·0	0·041	17·6 (2)	0·1
0 S.D.		1·7	16·1	1·6	0·89	0·019	4·6	0·35
Faceworker	11	54	62·9	(3) 7·0 (1)	2·2 (2)	(1) 0·034 (3)	17·7 (2)	1·6
S.D.		1·4	25·7	1·6	1·80	0·012	3·9	1·29
1 and 2	24	54	78·3	6·1	2·5 (3)	0·051	18·7 (3)	1·5
S.D.		1·5	26·6	1·7	1·31	0·028	4·8	1·19
3	11	54	70·1	6·1	2·0	0·042 (2)	19·5 (3)	1·5
S.D.		1·9	27·9	2·0	0·76	0·022	4·6	1·04
P.M.F.	14	54	68·1	7·3	2·1 (4)	0·037 (7)	16·5	1·6
S.D.		1·7	19·2	3·2	1·06	0·018	4·1	1·40
Significance All faceworkers compared with non-faceworkers			Not significant t test (66 d.f.) 1.562	t test (65 d.f.) 2·669 $P < 0·01$	Not significant	Not significant	Not significant	$\chi^2 = 9·11$ (8) (1 d.f.) $P < 0·01$

(1) Excluding subject No. 265
(2) 10 subjects only
(3) 23 subjects only
(4) 12 subjects only
(5) 9 subjects only
(6) 7 subjects only
(7) 11 subjects only
(8) Based on number of men without dyspnoea

The radiograph taken on the day of examination was classified by three observers independently and the final category was decided from these three opinions as described by McCallum and Browne (1955). The radiological categories used are those described by Fletcher, Mann, Davies, Cochrane, Gilson, and Hugh-Jones (1949).

Dyspnoea was assessed from the subject's account of his symptoms, and classified numerically (Fletcher, 1952).

Results

The results for the younger group are summarized in Table 3 and for the older group in Table 4 (Figs. 2 to 7). Statistical tests are summarized in Table 5.

Maximum Voluntary Ventilation.—Fig. 2 depicts the results of the test of maximum voluntary ventilation (M.V.V.) in all 105 miners and 10 controls, and the means in the different categories. In order to allow for the different ages and sizes of the subjects the results have been expressed as a percentage of the value predicted by the formula of Needham, Rogan, and McDonald (1954) who used the same method. In Tables 3 and 4 the results are expressed in litres per minute at ambient temperature and pressure. In miners the M.V.V. is lower than in non-miners, but this difference is not significant at the 5% level. Simple pneumoconiosis appears to have no effect on the M.V.V. In the subjects with simple pneumoconiosis the M.V.V. is not significantly lower than in the non-miners or non-faceworkers, and is actually higher than in faceworkers without pneumoconiosis. In all those with P.M.F., and in the young faceworkers without pneumoconiosis, however, the M.V.V. is significantly

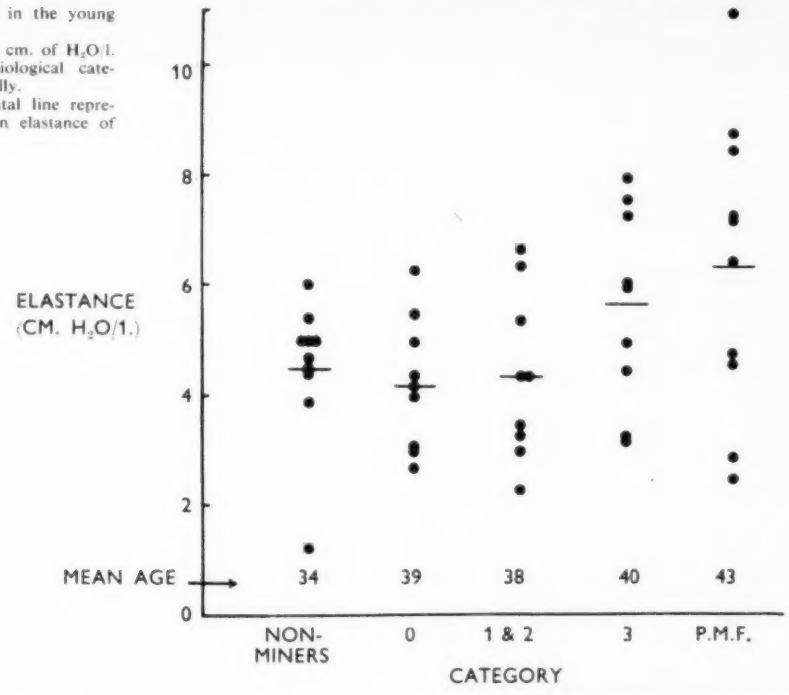


FIG. 3.—Elastance in the young group.
Elastance in cm. of H_2O/l. vertically, radiological category horizontally.
The horizontal line represents the mean elastance of each category.

reduced (Table 5). There is a trend of decreasing M.V.V. with increasing radiological abnormality. This is shown by both the old and the young group, but in neither case does the trend reach statistical significance ($P < 0.2$).

It will be seen in Fig. 2 that the mean M.V.V. of miners and non-miners alike has fallen below normal when expressed as a percentage of the predicted value. This is probably due to the fact that the prediction formula is based on the best of two or three attempts, while the result reported here is the mean of three.

Elastance.—The elastance reported here is the "functional" (dynamic) elastance which obtains during normal respiration, rather than the "static elastance". Figs. 3 and 4 depict the individual findings in the subjects arranged according to their radiological classification, together with the means of the different radiological groups. The means and standard deviations are also given in Tables 3 and 4 and can be compared with the mean elastance of normal individuals of 4·66 cm. H_2O/1. (mean of 303 observations reported in the literature by Bondurant, Hickam, and Isley, 1957; Butler and Smith, 1957; Butler, White, and Arnott, 1957; Cherniack, 1956; Frank, Mead, Siebens, and Storey, 1956; Marshall and Dubois, 1956a; McIlroy, Marshall, and Christie, 1954; Otis, Fenn, and Rahn, 1950). The published figures were not all obtained

TABLE 5
TESTS OF SIGNIFICANCE (t TEST)

Group	Test	Category	Compared with	Degrees of Freedom	t	P
Young men	M.V.V.F	0	Non-miners	17	2·214	< 0·05
		P.M.F.	Non-miners	17	2·262	< 0·05
	Elastance	0	Non-miners	17	0·468	Not significant
		P.M.F.	Non-miners	17	2·002	Not significant
		1 2 3	Non-miners	26	0·804	Not significant
Old men	M.V.V.F	0	Non-faceworkers	17	1·886	Not significant
		P.M.F.	Non-faceworkers	20	2·171	< 0·05
	Elastance	0	Non-faceworkers	16	3·478	< 0·01
		P.M.F.	Non-faceworkers	20	2·436	< 0.05
		1 2 3	Non-faceworkers	41	2·479	< 0·02
	Total non elastic work	0	Non-faceworkers	15	0·922	Not significant
		P.M.F.	Non-faceworkers	20	0·439	Not significant

by the method used in this paper, nor were they all in subjects of the same age ranges, but the different methods give results which fall within the range 2·7 to 11·1 and no definite association with age in adults has been established (Marshall, 1957; Butler *et al.*, 1957).

Amongst the younger men work underground is not associated with any significant alteration of pulmonary elastance. There is no convincing evidence that either simple pneumoconiosis or P.M.F. is accompanied by any such alteration. The apparent trend of increasing elastance with increasing radiological abnormality (Fig. 3) is suggestive but not statistically significant. Similarly the result in P.M.F. is not significantly higher than in the non-miners.

Amongst the older men the elastance is significantly higher in faceworkers than in non-

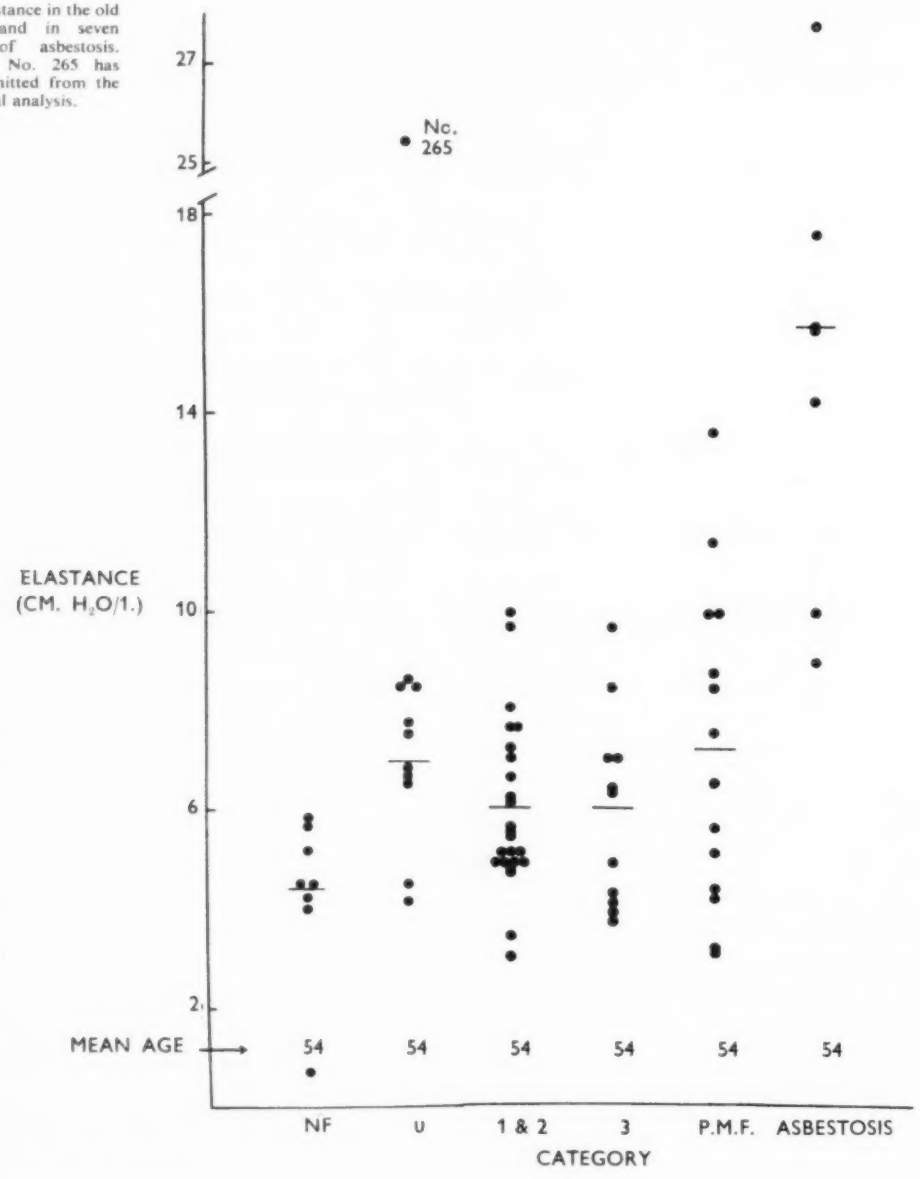


FIG. 4.—Elastance in the old group and in seven cases of asbestosis. Subject No. 265 has been omitted from the statistical analysis.

FIG. 5

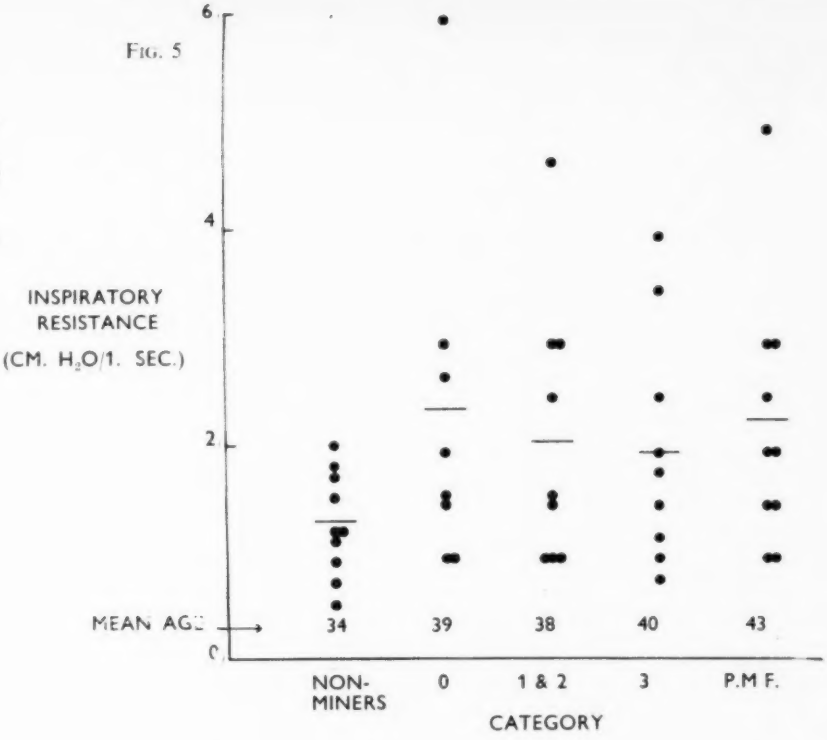


FIG. 5.—Inspiratory resistance in the young group.
The horizontal line represents the mean resistance of each category.

FIG. 6.—Inspiratory resistance in the old group.

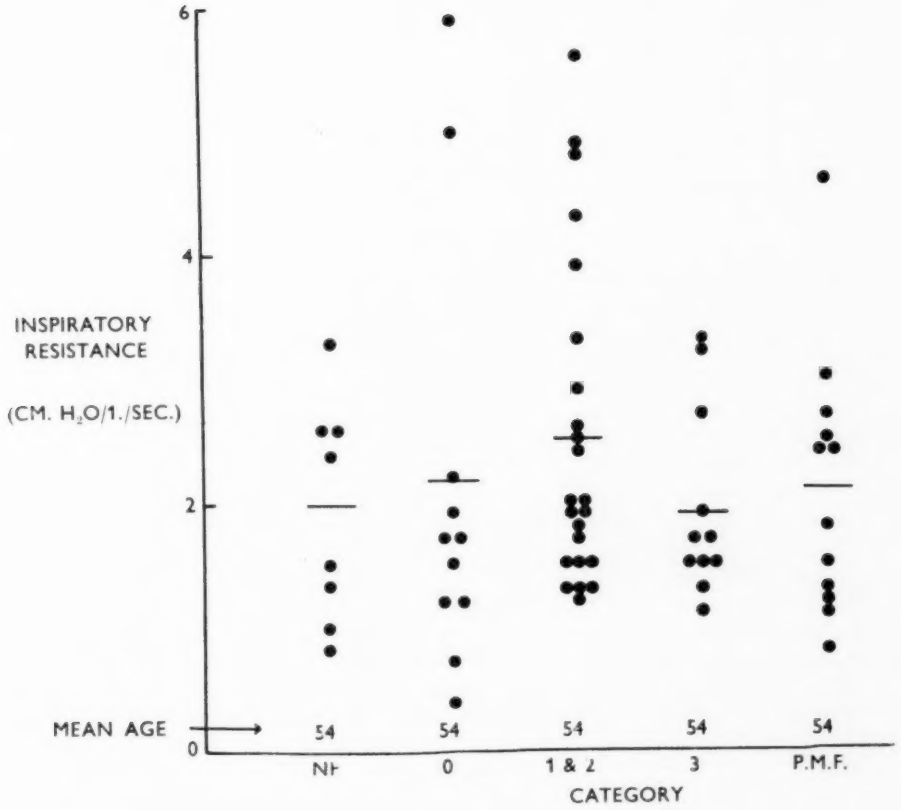


FIG. 6

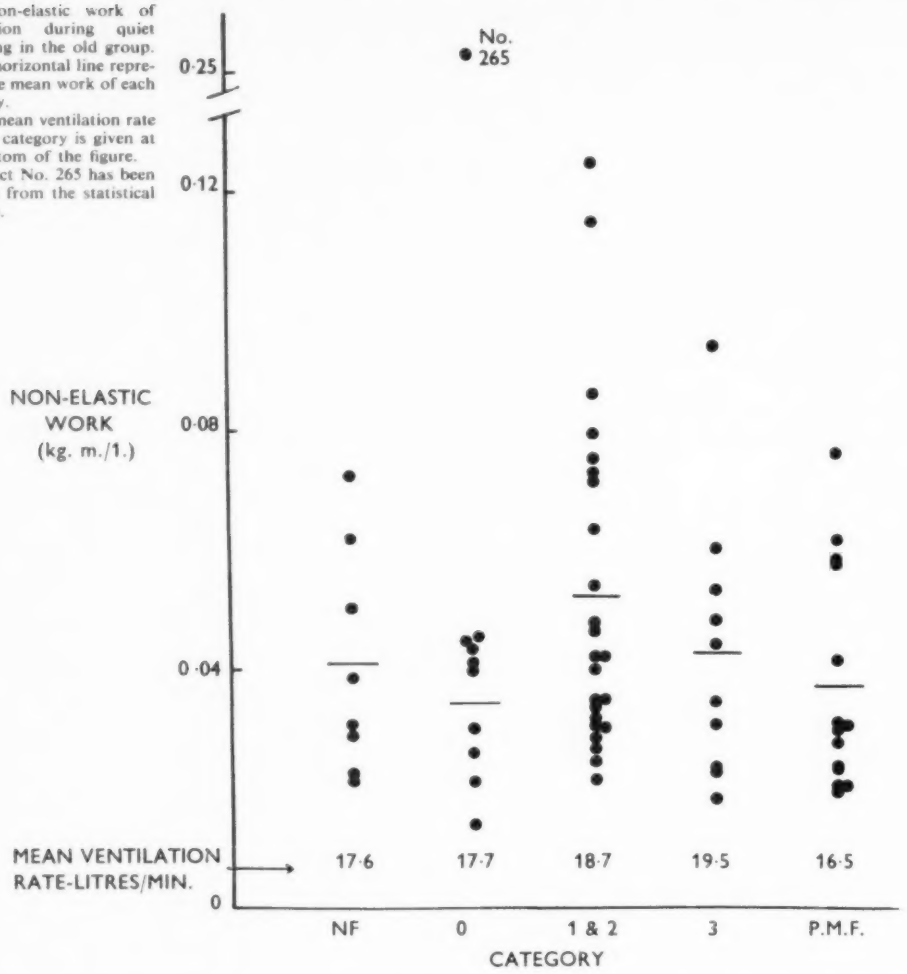


FIG. 7.—Non-elastic work of respiration during quiet breathing in the old group.
The horizontal line represents the mean work of each category.
The mean ventilation rate in each category is given at the bottom of the figure.
Subject No. 265 has been omitted from the statistical analysis.

faceworkers. It is significantly increased in simple pneumoconiosis, but it is increased even more in faceworkers without pneumoconiosis. In older men with P.M.F. the elastance is also significantly increased but it is no higher than in faceworkers without pneumoconiosis. If the older men are compared with the younger, elastance is found to be significantly higher among the older faceworkers without pneumoconiosis, and in categories 1 and 2. The difference between young and old is not significant in category 3 or in P.M.F. Amongst those men who have never worked at the face the elastance is the same in young and old.

Non-elastic Resistance.—Figs. 5 and 6 show the results for non-elastic resistance during inspiration, and the means and standard deviations are given in Tables 3 and 4. The mean can be compared with the mean resistance for normal subjects of 1·96 cm. H_2O/l./sec. (Mean of 69 determinations in normal subjects by this method: Marshall, 1957; Marshall and Dubois, 1956a; Mead, Lindgren, and Gaensler, 1955; Mead and Whittenberger, 1953.) One of these papers shows that there is a tendency for resistance to rise with age, but the highest resistance was only 2·9 cm. H_2O/l./sec. (Mead *et al.*, 1955). It can be seen that the young controls gave a significantly lower result than all the other subjects. The reason for this is unknown. All other subjects gave very similar results regardless of radiological abnormality.

Total Non-elastic Work.—The work of breathing was estimated only in the older subjects. In Fig. 7 and Table 4 non-elastic work is expressed in kilogram-metres per litre. Theoretically this is

directly proportional to resistance, if the flow pattern is constant. In fact the correlation coefficient between non-elastic work of inspiration (during which resistance remains relatively constant) and inspiratory resistance was + 0·65 ($P < 0.001$). Though work done per litre of air flow probably increases with increasing ventilation in each individual, it is a better basis for the comparison of individuals with different ventilation rates than the work done per minute, which has a much greater dependence on the minute-volume. Moreover it is difficult to predict the minute-volume from the record obtained during a single respiratory cycle, especially when there may be a pause between successive cycles. The ventilation rates recorded in this paper have been calculated without allowing for any pause, and consequently the figures are rather high. However, the mean ventilation rates in the different categories were similar, and the scatter about the mean was not great.

The individual and mean results shown in Fig. 7 may be compared with the mean for normal individuals of about 0·035 kg.m./l. This figure is seldom exceeded in subjects without dyspnoea. Unfortunately, very little information about non-elastic work of breathing has been published. Calculation from the formula of Otis *et al.* (1950), assuming ventilation at 20 breaths per minute, at 20 litres per minute, and a resistance of 1·96 cm. H_2O/l./sec., gives a figure of 0·029 kg.m./l. Butler (1957) quotes 0·0103 kg.m./l. in five normal subjects and calculations from the findings of McIlroy *et al.* (1954) give 0·029 kg.m./l. Cherniack (1956) found 0·0258 kg.m./l. in seven normal subjects. It seems probable, therefore, that the means in all older coalminers are slightly higher than normal. There is a trend of decreasing work with increasing radiological abnormality but this trend does not reach significance at the 5% level. Amongst those men without pneumoconiosis the non-elastic work was lower in the faceworkers than in those who had never worked at the coal-face, but this difference was not statistically significant.

Dyspnoea.—In Tables 3 and 4 is given the mean degree of subjective dyspnoea assessed by the numerical scale running from 0 to 5 described by Fletcher (1952). It will be seen that there was significantly less dyspnoea among the non-miners and those colliery employees who had never worked underground. There was no excess of dyspnoea in miners without pneumoconiosis. Amongst the older miners there was no association between dyspnoea and the radiological category of pneumoconiosis, but in the younger men there was a trend towards increasing dyspnoea with increasing radiological abnormality. This may have been a function of their increasing age. So few subjects complained of the severer grades of dyspnoea that further analysis of this symptom is not justified.

Discussion

In a study of this type the method of selection of the subjects is of fundamental importance (Carpenter *et al.*, 1956) and it must be admitted that in this study selection has not been ideal. The use of hospital patients adds to the difficulties of interpretation of the results. Though some attended simply for a routine radiograph of the chest, others had symptoms of chest disease. This group might therefore be expected to give abnormal results in the various tests. This does not, however, necessarily invalidate the comparison of the results in one radiological category with those in another, as there is reason to suppose that those with respiratory symptoms were equally distributed throughout the various categories (Newell and Browne, 1955). However, there was considerable difference in the mean age of the patients in the different radiological categories and this may influence the results. It would therefore be unwise to attach too much importance to the results obtained in these hospital patients, and they have been included only because they show a pattern similar to that obtained in the group of older men and thus lend some support to the conclusions drawn from this group.

The men in the older group were all about the same age and were selected randomly, but there was a high lapse rate and this could have affected the results. Moreover bias in the results could have been caused by selection of the men who originally attended for chest radiographs, the men from whom the random sample was taken. This point is discussed by McCallum and Browne (1955) who conclude that the sample of about 90% of the mining population is a representative one. It is possible that the more severely disabled men might have retired from mining before the radiological survey was carried out and this might have influenced in particular the composition of the group with progressive massive fibrosis, in whom symptoms were more severe. These men would have been 45-50 years of age at the time of the survey, which is early for complete incapacity, and it is believed that there cannot have been many men who had left mining for this reason. The sample which was investigated included four men who had left mining since the radiological survey.

The value of this work would have been greatly enhanced if it had been possible to investigate a reasonably large group of control subjects, in the age range 52-57. It had been hoped to collect

TABLE 6
COMPARISON OF M.V.V. IN ELDERLY MINERS AND NON-MINERS OBTAINED BY DIFFERENT AUTHORS

Author	Sample	Method	Non-miners	Radiological Category					
				0	1	2	3	P.M.F.	
								B	D
Gilson *et al.* (1955)	Selected miners and non-miners	Spirometer M.V.V.F	118(10)	94(8)	100(8)		81(8)	61(8)	33(8)
Mean age			54·3	54·0	54·2		54·9	55·1	55·0
Carpenter *et al.* (1956)	All working miners Colliery L	F.E.V. 0·75 Indirect M.B.C.	—	72·1(9)	88·2(6)	83·7(3)	72·0(1)	—	
Mean age				59·1	58·2	55·7	61·0		
Carpenter *et al.* (1956)	Three random population samples combined	F.E.V. 0·75 Indirect M.B.C.	88(134)	73·8(167)	90·3(12)	78·4(17)	76·8(55)	—	
Mean age			59·5	59·5	58·7	58·9	59·8		
Higgins *et al.* (1956)	Random population sample Leigh	F.E.V. 0·75 Indirect M.B.C.	85·0(84)	76·0(101)	91·5(6)	86·0(7)	79·8(8)	73·6(10)	
Mean age			59·4	59·1	57·3	59·0	58·8		
Present investigation*	Random sample of working miners	Bag and valve-box M.V.V.F	94(8)	69(11)	78(7)	89(17)	77(11)	75(14)	
Mean age			54·1	54·4	53·6	54·5	54·2	54·4	

*Experimental results have been multiplied by 1·1 to make them comparable with the results of other workers.
In this table figures in parenthesis refer to the number of men who contributed to the mean figure which is quoted.

subjects from another industry in this area but the number of men who were prepared to undergo tests was too small to make this worthwhile. It has therefore been necessary to rely on normal values reported in the literature.

Maximum Voluntary Ventilation.—The results of this investigation confirm and extend those of Carpenter *et al.* (1956), who also found a surprisingly low mean M.V.V. in elderly miners without pneumoconiosis, although they used a different method. Their results were expressed at B.T.P.S. by multiplying by 40 the mean volume of air expelled in three-quarters of a second during three or four forced expirations (the time being measured after the expulsion of the first 100 ml.). This correlates well with M.V.V. recorded with a spirometer (Kennedy, 1953). The M.V.V.s reported in this paper are expressed at ambient pressure and temperature, and consequently are all rather lower than those reported by Carpenter *et al.* In Table 6 the results in the older group reported here have been multiplied by 1·1 to bring them approximately to B.T.P.S. and are compared with the findings of several other authors. The group most closely resembling the men in this investigation are the working miners in Colliery L. The subjects of the present investigation gave results very similar to these men and to the other random samples, the chief difference being the lower figure in Category 1 and the higher figure in Category 2. Gilson and Hugh-Jones (1955) report much higher figures in non-miners and in simple pneumoconiosis, but lower ones in P.M.F. The high figures are probably due to the method used, as they recorded the volume with a spirometer, which, they demonstrated, tends to over-estimate in the intermediate ranges. The low figures in P.M.F. are probably the result of their investigating subjects with more advanced disease. In the present work the majority of subjects had either Category A or B of P.M.F. (Table 7), but if only cases of P.M.F. Category B are considered the mean M.V.V. is still as high as 73·2 (about 80 at B.T.P.S.) l./min. Amongst the men with P.M.F. investigated by Higgins, Oldham, Cochrane, and Gilson (1956) nine out of the 10 were in category A or B (Higgins, 1958) and their results were very similar to the present investigation.

All authors agree that the M.V.V. is lowered in P.M.F. They also agree (Table 6) that elderly miners without pneumoconiosis have a lower M.V.V. than those with simple pneumoconiosis, categories 1 and 2, and lower than non-miners. The possible reasons for this are discussed by Carpenter *et al.* (1956) who

TABLE 7
RADIOLOGICAL CATEGORY OF P.M.F.

Younger Men		Older Men	
Case No.	Radiograph	Case No.	Radiograph
138	3 C6/6	209	3 B2/1
142	3 A4/2	210	2 B2/0
144	3 B2/4	245	2 A2/1
162	3 A3/3	250	3 A3/4
165	3 A5/1	253	2 B4/1
167	3 B3/0	254	3 B5/4
173	3 A3/4	256	3 A1/1
175	3 C4/4	257	3 B4/1
177	3 B3/3	264	3 A4/4
178	3 B4/4	282	2 A0/1
		285	3 B5/5
		299	2 A4/2
		300	3 B4/3
		306	3 D4/2

conclude that generalized emphysema may account for it. The present investigation has not provided statistically significant confirmation of their demonstration that simple pneumoconiosis also lowers the M.V.V.

Pulmonary Elastance.—There is wide scatter of the results obtained in each radiological category. It is believed that this is not due to deficiencies of the method, but represents true differences between individuals, because there was good agreement between the elastance of 65 subjects measured by two different methods, and because the method does demonstrate considerable abnormality in asbestosis (Fig. 4). Moreover in the non-miners and non-faceworkers the mean elastance is close to the figure previously reported in normal men.

In the younger group the mean age increases with increasing severity of radiological abnormality and this throws some doubt on the relationship between radiological category and elastance observed, but no association with age could be demonstrated within each category, or in the whole of the younger group. Also Frank *et al.* (1956) reported no association with age over a similar age range, in normal individuals. There is no evidence that differences in body build are responsible for differences in elastance in these men, since correlation between height and elastance, within each radiological category, was demonstrable only in the young men in category 3. Such a correlation was found to occur in normal men (Marshall, 1957).

Since the elastance of those older men who have never worked at the coalface is the same as that of the young men who have never worked in a coalmine, the higher elastance of the older faceworkers must be mainly due to their having worked underground for longer than the young men. This is substantiated by the observation that in Category O, where the difference between young and old is most marked, the old men had, on the average, worked underground for 14 years longer than the young men, though the time spent on the coalface was only two years more.

The finding of a raised elastance in elderly faceworkers without pneumoconiosis also suggests that this change is brought about by work underground rather than by radiological pneumoconiosis.

These men, together with those who have P.M.F., form the groups in which M.V.V. is abnormally low, and elastance is abnormally high. In individual cases, however, there is no correlation between M.V.V. and elastance, which makes it difficult to accept the rather high elastance as a cause for the reduction of M.V.V.

It should be stressed that in only two out of the 97* miners did the elastance exceed the upper limit of normal, which Frank *et al.* (1956) put at 11·1 cm. H_2O/l. Alterations of elastance of this order have been recorded in hypertrophic emphysema (Attinger, Goldstein, and Segal, 1956; Cherniack, 1956; Mead *et al.*, 1955; Stead, Fry, and Ebert, 1952), and this may account for the changes demonstrated in these coal-miners. The changes in elastance in coal-miners are not, therefore, a cause of disability but are a pointer towards the nature of the lesion responsible for it.

The finding of a virtually normal elastance in the presence of massive fibrosis of the lung was unexpected. In this type of pneumoconiosis the fibrosis is not generalized but localized to well-defined areas, which, in these subjects, were never very extensive. Presumably these areas do not expand during a normal inspiration and consequently make no direct contribution to the elastance, while the elastance of the remaining lung, which does expand during inspiration, is, at any rate during quiet breathing at rest, apparently close to normal. This does not exclude the possibility that there may be an increase of elastance during deep inspiration and at larger lung volumes.

Non-elastic Resistance.—The mean non-elastic resistance is normal in these coal-miners. Marshall and Dubois (1956b) report a moderate increase of non-elastic resistance in their single case of anthracosis (aged 57) but this falls well within the range depicted in Fig. 6.

The inspiratory resistance does not correlate with the maximum voluntary ventilation nor with the maximum flow-rate during forced inspiration or expiration. Resistance is not necessarily constant throughout inspiration (Dayman, 1951) but the records have been analysed in such a way as to minimize this defect. Mead and Whittenberger (1953) reported that the pressure flow curve delineated by their method was parabolic, but in this work it was found to be more nearly linear. (The resistance reported here corresponds to K_1 of Mead and Whittenberger.) If the records were really parabolic, treating them as linear between flow rates of 0 and 60 l./min. would tend to give too high a value to the resistance. Since the values obtained are no higher than those previously reported for normal individuals (and in the controls they are actually lower) this method of interpretation cannot have caused a very serious error. As total non-elastic resistance is normal during quiet inspiration it must be assumed that neither airway resistance nor tissue resistance

*Subject 306, elastance 13·6; subject 25A, elastance 11·4 (see Table 6).

can have altered much. It has previously been shown that tissue resistance was not altered in a case of anthracosis (Marshall and Dubois, 1956b).

It appears that the radiological abnormality of pneumoconiosis is not associated with any narrowing or distortion of the airways demonstrable during quiet inspiration. Nor does this occur in miners without pneumoconiosis. This does not exclude the possibility that such distortion may occur during expiration, or may be manifest at faster flow rates during inspiration. Account is taken of these possibilities in the measurement of non-elastic work of respiration. For example, in subject 265 inspiratory resistance was 5·9 cm. H_2O/l./sec. at slow flow rates but rose to 21·8 during fast inspiration and to 40·7 cm. H_2O/l./sec. during fast expiration. Total non-elastic work was very high, 0·253 kg.m./l., at a ventilation rate of 14 litres per minute.

Non-elastic Work of Respiration.—The non-elastic work of breathing is a measure of integrated airways resistance. It was highest in Category 1 and 2, being 0·040 kg.m./l. in Category 1 and 0·055 kg.m./l. in Category 2. It was lower in Category 3 and nearly normal in P.M.F. The pattern presented by the means of the individual results in the various categories was remarkably similar to the pattern of mean M.V.V. in the same men (Figs. 2 and 7), low M.V.V. occurring with low non-elastic work. It had been supposed that a low M.V.V. would be accompanied by high non-elastic work, and this unexpected finding requires further consideration.

Non-elastic work was measured during relatively quiet respiration and might not necessarily correlate very well with reduction of a maximum ventilatory effort. However, correlation of the two has been reported by Cherniack (1956) in cases of emphysema and in the present investigation a significant, but small, negative correlation between non-elastic work and M.V.V. was established ($r = -0{\cdot}312$). Nevertheless the mean non-elastic work in different radiological categories shows a positive correlation with M.V.V. This could be entirely fortuitous but could be explained in one of the following ways. First, there are theoretical reasons for supposing that a high pulmonary elastance helps to maintain patency of the airways, and high elastance was demonstrated in the two groups who give low figures for non-elastic work. There was not, however, any correlation between elastance and non-elastic work, either in these two groups or in the series of miners as a whole, so that this would appear not to be the explanation. Secondly, non-elastic work done on the lung is not equal to the total non-elastic work done by the subject. A variable proportion of the total is required to move the chest wall and diaphragm. If the proportion of the available power which goes to move the thoracic walls is increased in certain individuals, then in these one might expect to see a reduction in the work done on the lung during normal ventilation accompanied by a reduction in maximum ventilatory ability. In these individuals the M.V.V. would be limited by excessive frictional resistance in the chest wall rather than by resistance in the airways; such is the picture presented by the faceworkers without pneumoconiosis, and by miners with P.M.F.

A rather similar observation has been made by Gandevia and Prime (1957) who found that the maximum intrathoracic pressure during a forced expiration in 10 patients with asthma or chronic bronchitis was reduced by inhalation of isoprenaline. They suggest that this may be due to limitation of the speed with which the chest wall can move. Similarly McKerrow, McDermott, Gilson, and Schilling (1958), measuring the airways resistance in cotton workers during expiration at high flow rates, found that alterations in the indirect M.B.C. and airways resistance are not very highly correlated, suggesting that airways resistance is not the sole factor limiting a maximum expiratory effort. A limitation of the speed of movement of the chest wall would not be recognized by measuring the maximum static pressure which can be sustained by the expiratory muscles. This has been shown (Carpenter *et al.*, 1956) to be unrelated to the M.V.V. in miners.

It is suggested, therefore, that in some miners the M.V.V. is limited by frictional resistance in the chest wall, rather than in the lungs, and that this occurs particularly frequently in faceworkers without pneumoconiosis, and in those with P.M.F. It appears to be responsible for the low mean M.V.V. obtained in these men.

In the majority of miners, however, airways resistance is the limiting factor and this accounts for the negative correlation between non-elastic work and M.V.V. recorded in these subjects and between airways resistance and M.V.V. recorded by McDermott (quoted by Carpenter *et al.*, 1956).

If non-elastic work, expressed in kilogram-metres per litre, is taken as a measure of the mean non-elastic resistance, as has been suggested in this paper, then in those miners without pneumoconiosis the non-elastic resistance appears to be highest in those men who have never worked at the coalface. This is misleading, and the probable reason why non-elastic work is lower in the faceworkers is because of an alteration in the flow pattern of respiration such that a steady low rate of flow throughout inspiration and expiration replaces the normal pattern of periods of high flow alternating with periods of negligible flow. This alteration could be imposed by frictional

resistance in the chest wall. Unfortunately no records of flow patterns were taken in these subjects and this suggestion cannot be confirmed. An alteration of the flow pattern of this type has been reported in asthma and in emphysema (Silverman, 1946), and it is possible that emphysema is responsible for the alterations in work, and the inferred alteration in flow pattern, in elderly faceworkers without pneumoconiosis and in those with P.M.F. Thus the conclusions of this investigation are not inconsistent with the suggestion of Carpenter *et al.* (1956) that the ventilatory capacity is low in miners without pneumoconiosis because they suffer from emphysema; it is implied that the same defect is also present in P.M.F.

Conclusions

This investigation has confirmed that P.M.F. is accompanied by a significant reduction in ventilatory ability, and that coal miners without radiological pneumoconiosis are similarly handicapped when compared with non-miners. In minor degrees of simple pneumoconiosis, however, there is no restriction of ventilation.

In accord with this the lungs were found to be stiffer than normal in P.M.F. and in elderly miners without pneumoconiosis. They were also slightly stiffer than normal in simple pneumoconiosis. It is felt that this stiffening of the lungs is not due directly to radiological pneumoconiosis but is brought on by long years of work underground. The deviation from normality was so small that this stiffening by itself is not considered to be of any clinical significance. It is not the cause of the reduction of ventilatory ability in these men, there being no demonstrable association between stiffness of the lungs and maximum voluntary ventilation.

In most of the men who have reduced powers of ventilation this is due to obstruction of the airways. This obstruction is seldom present during a normal inspiration but develops during the later stages of expiration (Fig. 1).

In some cases the reduction of M.V.V. cannot be explained in this way. It appears to be due to excessive stiffness of the chest wall. This occurs particularly frequently in elderly coal-miners without pneumoconiosis and in P.M.F. It may be the result of the distortion of the chest wall which accompanies emphysema. The results of the other tests are also consistent with the presence of emphysema in all those men who have a reduction of ventilatory ability, whether pneumoconiosis can be demonstrated on the radiograph or not.

I wish to express my thanks to Professor R. C. Browne for permission to examine his patients, and for encouragement and advice. I also wish to thank Mr. D. J. Newell for the statistical analyses, Mrs. D. Weightman for the preparation of the figures, the National Coal Board for financial assistance, and Mr. E. Richardson who designed and built some of the apparatus.

References

Attinger, E. O., Goldstein, M. M., and Segal, M. S. (1956). *Amer. Rev. Tuberc.*, **74**, 210.
Bondurant, S., Hickam, J. B., and Isley, J. K. (1957). *J. clin. Invest.*, **36**, 59.
Butler, J. (1957). Personal communication.
——, and Smith, B. H. (1957). *Clin. Sci.*, **16**, 125.
——, White, H. C., and Arnott, W. M. (1957). *Clin. Sci.*, **16**, 709.
Carpenter, R. G., Cochrane, A. L., Gilson, J. C., and Higgins, I. T. T. (1956). *Brit. J. industr. Med.*, **13**, 166.
Cherniack, R. M. (1956). *J. clin. Invest.*, **35**, 394.
Dayman, H. (1951). *Ibid.*, **30**, 1175.
Dornhorst, A. C., Semple, S. J. G., and Young, I. M. (1953). *Lancet*, **1**, 370.
Fletcher, C. M. (1952). *Proc. roy. Soc. Med.*, **45**, 577.
——, Mann, K. J., Davies, I., Cochrane, A. L., Gilson, J. C., and Hugh-Jones, P. (1949). *J. Fac. Radiol. (Lond.)*, **1**, 40.
Frank, N. R., Mead, J., Siebens, A. A., and Storey, C. F. (1956). *J. appl. Physiol.*, **9**, 38.
Gandevia, B. H., and Prime, F. J. (1957). *Thorax*, **12**, 358.
Gilson, J. C., and Hugh-Jones, P. (1955). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 290.
Higgins, I. T. T. (1958). Personal communication.
——, Oldham, P. D., Cochrane, A. L., and Gilson, J. C. (1956). *Brit. med. J.*, **2**, 904.
Kennedy, M. C. S. (1953). *Thorax*, **8**, 73.
Lilly, J. C. (1950). *Meth. Med. Res.*, **2**, 113.
Marshall, R. (1957). *Clin. Sci.*, **16**, 507.
——, and Dubois, A. B. (1956a). *Ibid.*, **15**, 161.
————— (1956b). *Ibid.*, **15**, 473.
McCallum, R. I., and Browne, R. C. (1955). *Brit. J. industr. Med.*, **12**, 279.
McIlroy, M. R., Marshall, R., and Christie, R. V. (1954). *Clin. Sci.*, **13**, 127.
McKerrow, C. B., McDermott, M., Gilson, J. C., and Schilling, R. S. F. (1958). *Brit. J. industr. Med.*, **15**, 75.
Mead, J., Lindgren, I., and Gaensler, E. A. (1955). *J. clin. Invest.*, **34**, 1005.
——, and Whittenberger, J. L. (1953). *J. appl. Physiol.*, **5**, 779.
Needham, C. D., Rogan, Mary C., and McDonald, I. (1954). *Thorax*, **9**, 313.
Newell, D. J., and Browne, R. C. (1955). *J. Fac. Radiol. (Lond.)*, **7**, 20.
Otis, A. B., Fenn, W. O., and Rahn, H. (1950). *J. appl. Physiol.*, **2**, 592.
Silverman, L. (1946). *J. industr. Hyg.*, **28**, 183.
Stead, W. W., Fry, D. L., and Ebert, R. V. (1952). *J. Lab. clin. Med.*, **40**, 674.

Brit. J. industr. Med., 1959, **16**, 166.

FURTHER STUDIES OF THE NEUTRALIZATION OF SILICA TOXICITY *IN VITRO*

BY

J. MARKS

From the Central Tuberculosis Laboratory, The Parade, Cardiff

(RECEIVED FOR PUBLICATION SEPTEMBER 5, 1958)

A previous paper (Marks, 1957) describes work done on a number of substances to ascertain their protective effect on phagocytic cells in tissue culture against injury by silica dust. The most potent of those investigated was 48-80, a drug used in experimental pharmacology to release histamine from mast cells.

In the present paper, several drugs related to compound 48-80 have been examined for their capacity to protect phagocytic cells against the toxic effect of silica dust *in vitro*. It is shown that protection can be dissociated from histamine-releasing activity in these compounds.

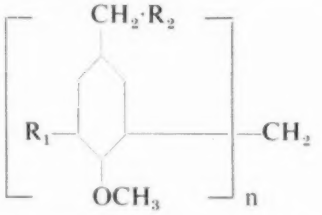
Other substances found to neutralize the toxicity of silica dust were certain phenazines, complexes of aluminium with chelating agents, and the histamine-releasing agent L 1935.

Tissue culture offers a convenient means of studying the injury of phagocytic cells by silica dust and their protection by suitable antagonists. In an earlier communication (Marks, 1957), a number of protective agents investigated in this way were described, of which the most potent was compound 48-80, a drug used in experimental pharmacology to release histamine from mast cells. Compound 48-80 was subsequently shown to protect mice against the fibrogenic action of silica dust (Marks, James, and Morris, 1958). Only small amounts of this drug are tolerated by man and therefore certain related compounds have been investigated in order to determine whether the properties of histamine-release and neutralizing action on silica are distinct. The drugs of this series were prepared in the Wellcome Research Laboratories, New York, where their effect on mast cells was assayed by Dr. Stata Norton using her published technique (Norton, 1954). In addition, the histamine-releasing agent L 1935 (Feldberg and Lecomte, 1955) was examined for protective activity.

A number of drugs unrelated to histamine release were included in the present investigations. Phenazine compounds studied in relation to experimental tuberculosis by Barry, Conalty, and Gaffney (1956) and Barry, Belton, Conalty, Denneny, Edward, O'Sullivan, Twomey, and Winder (1957) were selected because their structure suggested the possibility of protective activity, and, in addition, three chelates of aluminium with dextran, sequestric acid and oxytetracycline respectively were prepared and tested.

Materials and Methods

The effect of silica and its antagonists on phagocytic cells was studied in tissue culture chiefly using the dehydrogenase technique described by Marks and James (1959). With this technique cells are incubated for three days with dust and their vitality then determined by their capacity to reduce tetrazolium. The dust used in the present work was a single sample of silica (tridymite) provided by Dr. G. Nagelschmidt, of the Safety in Mines Research Establishment, Sheffield. Its mean volume surface diameter was 1·3 microns and specific surface 2·5 m.²/g. The essential structure of the compounds which were related to 48-80 was as follows:—

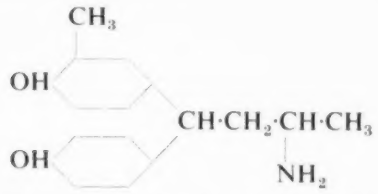


(The radicals R_1 and R_2 and values of n are listed in Table 1.)

Compound 46-150 differed from the remainder in that its nitrogen was quaternary. Solutions of these drugs and also L 1935 were made aseptically in Ringer's solution freshly for each experiment.

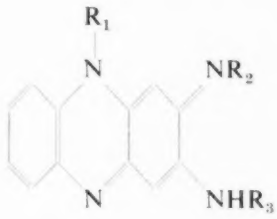
A quantity of L 1935 was obtained for examination through the courtesy of Dr. B. N. Halpern and Dr.

Dinah M. James. It is a mixture of the following compound and its dehydro form:—

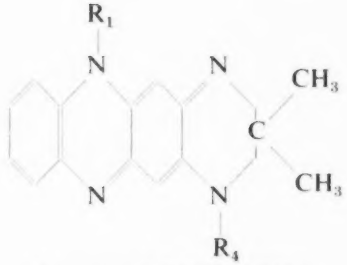


The general structures of the phenazines studied were as follows:—

1



2



(compounds B621 and B654)

The compounds listed below were examined.

The phenazines were prepared for use by dissolving them in hot ethanol at a concentration of 0·1%. Solution was assisted in several cases by acidification with HCl, but in a number a small proportion of the drug remained insoluble. Shortly before use, 1 in 10 dilutions of the ethanolic solutions were made in 25% serum-tyrode solution.

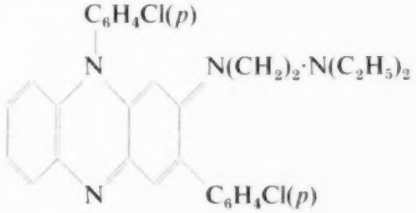
The aluminium chelates were prepared by mixing 1 ml. volumes of 1% $AlCl_3 \cdot 6H_2O$ with 4·8 ml. of 5% clinical dextran, 1·5 ml. of 1% di-sodium diaminoethane-tetra-acetic acid (sequestric acid), or 2·5 ml. of 0·1% oxytetracycline. Each mixture was neutralized with 0·1*N* NaOH and its volume made up to 10 ml. with isotonic saline.

Results

Compounds Related to 48-80.—Compound 46-107, which appears to be relatively harmless to mast cells, proved to be twice as effective as 48-80 in protecting phagocytic cells against the toxic effect of silica dust. Compounds 46-108 and 47-30 were approximately four times less effective than 48-80 and the quaternary compound 46-150 appeared devoid of protective action. The results recorded in Table 1 are representative of those obtained in six experiments in which the dehydrogenase method of assessing cell vitality was used. Table 1 includes details of the structure of the compounds and of their destructive effect on mast cells relative to that of 48-80 which is taken as 100. The control cell cultures had a mean dehydrogenase activity of 50 arbitrary units but cultures exposed to silica dust an activity of only 4 units. The ability of the drugs studied to protect cells against silica injury is shown in Table 1 by the degree to which dehydrogenase activity was main-

Number	R_1	R_2	R_3	R_4
B283	Phenyl	H	Phenyl	—
B430	Cyclohexyl	Cyclohexyl	H	—
B595	Phenyl	Phenyl	H	—
B629	p-Chlorophenyl	p-Chlorophenyl	H	—
B663	p-Chlorophenyl	$CH(CH_3)_2$	p-Chlorophenyl	—
B673	p-Chlorophenyl	Cyclohexyl	p-Chlorophenyl	—
B740	p-Chlorophenyl	Cycloheptyl	p-Chlorophenyl	—
B778	Phenyl	C_2H_4OH	Phenyl	—
B782	p-Chlorophenyl	C_2H_4OH	p-Chlorophenyl	—
B621	Phenyl	—	—	Phenyl
B654	p-Chlorophenyl	—	—	p-Chlorophenyl

An additional compound, B749, with the following structure was also investigated.



tained in their presence. Some of the cultures treated with 46-107 in this experiment gave high readings but the divergence from the mean control was not outside the range of variation met in control cultures nor especially characteristic of the drug. Compound 46-107 was also found to be protective in tissue culture when glucose consumption and morphological criteria of cell damage were employed (Marks, 1957). Despite its histamine-releasing activity, compound 48-80 was tolerated by cells in

TABLE 1

PROTECTION OF PHAGOCYTIC CELLS AGAINST EFFECT OF SILICA DUST BY COMPOUNDS RELATED TO 48-80

Drug	Dehydrogenase Activity* of Cultures after Addition of 20 µg. Dust and Stated Quantity of Drug (µg.)					Polymerization and Radicals (see text)			Effect on Mast Cells
	40	20	10	5	2·5	n	R_1	R_2	
46-107	—	77	82	69	31	2	CH_3	$CH_2N(CH_3)_2$	0
48-80	55	56	51	27	—	2-4	H	CH_2NHCH_3	100
46-108	43	26	13	—	—	2	H	CH_2NHCH_3	2
47-30	38	29	14	—	—	2-3	H	$NHCH_3$	20
46-150	8	6	6	—	—	2	CH_3	$CH_2NI(CH_3)_2$	< 5
Nil	Mean dehydrogenase activity = 4 units (untreated dust)								

*Arbitrary units.
The mean dehydrogenase activity of undusted control cultures was 50 units.

somewhat higher concentrations than compound 46-107.

For convenience, drugs were added to the cultures at the same time as the dust in most experiments but in some cells and dust were incubated together for six hours before drugs were added, a period found sufficient to permit phagocytosis. The results in the latter conditions (Table 2) were similar to those in the former, indicating in agreement with previous observations on compound 48-80 (Marks, 1957) that protection of the cells from injury by silica dust was not due to interference with phagocytosis.

TABLE 2

PROTECTION OF CELLS AGAINST EFFECT OF SILICA DUST BY ANTAGONISTS ADDED AFTER AN INTERVAL

Drug Preparation	Amount of Dust per Culture (µg.)	Dehydrogenase Activity with Stated Dose of Drug Preparation (µl.)		
		80	40	20
B283 phenazine, 0·01%	20	14	24	20
B673 phenazine, 0·01%	20	21	16	12
B749 phenazine, 0·01%	20	26	40	20
B778 phenazine, 0·01%	20	42	28	26
Oxytetracycline chelate of aluminium (0·011% aluminium)	20	41	38	36
Compound 46-107, 0.05%	20	45	39	47
Nil	20	Mean activity = 1 unit (untreated dust)		
Nil	Nil	Mean activity = 37 units (controls)		

Cells and dust were incubated together for six hours at 37°C. before antagonists were added. Readings were made after a further three days' incubation.

Compound L 1935.—A comparison was made between this drug and the 48-80 series in four dehydrogenase experiments. It was found to be approximately half as active as 48-80 in protecting cells against the effect of silica dust.

Phenazines.—Of the phenazines examined, only B283, B673, B749, and B778 exhibited appreciable protective activity, the last two being the most effective. A comparison of their effect with that of compound 46-107 and an aluminium complex is recorded in Table 2. Protection by the phenazines appeared more obvious with the dehydrogenase technique than with the two other methods referred to above. An artefact appeared to be excluded, however, by the observation that phenazines were without effect when added at the same time as tetrazolium to cultures previously incubated with dust.

Aluminium Complexes.—The capacity of these compounds to protect cells against silica dusts was very similar to that of inorganic aluminium salts in equivalent concentration. The oxytetracycline complex was the most effective and the sequestric acid complex the least. A comparison made in a representative experiment is recorded in Table 3.

TABLE 3

PROTECTION OF CELLS AGAINST EFFECT OF SILICA DUST BY DIFFERENT ALUMINIUM COMPOUNDS

Compound Added	Amount of Dust per Culture (µg.)	Dehydrogenase Activity with Stated Dose of Aluminium (µg. metal per culture)		
		8·8	2·2	0·55
Aluminium chloride	40	27	17	10
Al-sequestric acid complex	40	25	13	6
Al-dextran complex	40	32	10	8
Al-oxytetracycline complex	40	44	26	7
Nil	40	Mean activity = 2·5 units (untreated dust)		
Nil	Nil	Mean activity = 44 units (controls)		

Discussion

Tissue culture techniques offer the advantages of convenience and speed in screening drugs for potential neutralizing action on silica dust. It is unlikely that they would fail to detect an agent of therapeutic value. However, the protective activity of a drug *in vitro* is not always reproduced *in vivo*. There are many possible reasons for such failures, for example, the agent may be destroyed, excreted, modified, or sequestrated in the intact animal before it reaches the dust-laden phagocyte in an effective form. From the results obtained with compound

48-80 (Marks *et al.*, 1958) and incomplete animal experiments on the drugs described above, it appears that some at least of the compounds selected for their activity *in vitro* offer the possibility of arresting the pathological processes of silicosis. The chief requirement now for progress in this field is a programme of synthesis of compounds suitable for study.

Experience with compound 46-107 has shown that histamine-release and neutralizing activity for silica can be dissociated. It is possible, therefore, that the 48-80 series of compounds may provide a drug of practical value. The protective activity of the phenazines is less well established since it appeared to be much greater with the dehydrogenase technique than with others. Although no artefact was detected, suspicion must remain that part at least of the apparent protection was spurious. Aluminium by inhalation has been used for a considerable period for the prevention and treatment of silicosis. The complexes of aluminium studied in the present work were prepared for possible systemic treatment with the object of reaching dust-laden cells not accessible to inhaled aluminium dust. Aluminium therapy is attractive in that its effect on silica would probably be more lasting than that of a wholly organic compound which would presumably be liable to chemical alteration. However, preliminary results suggest that the aluminium complexes are less effective than organic compounds in short-term animal experiments and are not innocuous themselves. (It is hoped to report later on the use in mice of the more important of the compounds described in the present work.)

This work was made possible by the generous provision of drugs by Dr. Stata Norton and Dr. E. de Beer of the Wellcome Research Laboratories, New York, and by Dr. V. C. Barry, Dublin. Dr. B. N. Halpern kindly provided a sample of L 1935 and Glaxo Laboratories Ltd. the therapeutic dextran. I am obliged to the Medical Research Council for a grant for apparatus and to Mr. P. J. Patterson for his technical assistance.

References

Barry, V. C., Conalty, M. L., and Gaffney, Ethna E. (1956). *J. Pharm. (Lond.)*, **8**, 1089.
——, Belton, J. G., Conalty, M. L., Denneny, J. M., Edward, D. W., O'Sullivan, J. F., Twomey, D., and Winder, F. (1957). *Nature (Lond.)*, **179**, 1013.
Feldberg, W., and Lecomte, J. (1955). *Brit. J. Pharmacol.*, **10**, 254.
Marks, J. (1957). *Brit. J. industr. Med.*, **14**, 81.
——, and James, Dinah M. (1959). *J. Path. Bact.*, 77, 401.
——, ——, and Morris, T. G. (1958). *Brit. J. industr. Med.*, **15**, 1.
Norton, Stata (1954). *Brit. J. Pharmacol.*, **9**, 494.

MISCELLANEA

The Employment of Diabetics

JOHN F. COPPLESTONE

From the Department of Health, Dunedin, New Zealand

(RECEIVED FOR PUBLICATION JULY 24, 1958)

Few studies have been made of the employability of diabetics, and recommendations concerning their employment are usually based on general principles. It is often considered that diabetics who are taking large doses of insulin should not be given work in which hypoglycaemic attacks might result in injury to themselves or others. However, the severity of an insulin reaction is now known not to be commensurate with the extent of hypoglycaemia; the dosage of insulin has no relationship to liability to reactions.

A survey has been undertaken of the employment experience during the preceding five years of 88 diabetics who attended the Dunedin Clinic during four months of 1957. There was some tendency for diabetics to take sedentary work. The occurrence of insulin reactions did not handicap these patients in varied types of occupations nor in driving vehicles, nor was there any evidence of an increased number of accidents in those who were liable to insulin reactions. Only about half the employed diabetics regularly carried an identification card: several, including two who were liable to severe reactions, had kept their condition secret from their employers and fellow employees.

It is concluded that the employment of diabetics needs to be limited only by their stamina, the presence of complications, and by their own good sense. Owing to the lack of objective information on the employment of diabetics it is urged that further surveys should be undertaken with the object of freeing diabetics from needless restrictions.

The prevalence of diabetes mellitus has been variously estimated at between 0·5 and 2% of the population in Great Britain and the United States. No figures of prevalence are available for New Zealand, but on this basis it might be expected that at least 3,000 diabetics are in gainful employment there. The problem of the hazards that diabetics may cause to themselves and their fellow workers is therefore important.

On diagnosis consideration must be given to the effect that the disease will have on the daily life of the patient, for the diabetic, more than most, must learn to live with his disease. The patient must necessarily rely on the advice of his doctor and this advice should not be lightly given where the occupation of the patient is concerned. Most published papers have been based on general principles, bearing in mind the possible complications of the disease and its treatment. In the United States, definite standards for employment were laid down by the American Diabetes Association in 1952. These state, *inter alia*, that the diabetic should be under regular medical care with an annual physical examination, that his condition should be known to his employer and key personnel, that he should always carry an identification card or tag, and that:

> " Diabetics are capable of performing any type of work for which they are physically, mentally, and educationally equipped. Those diabetics who are taking large doses of insulin should not, however, be assigned work in which hypoglycaemic attacks may result in injury to themselves or others."

The danger of the hypoglycaemic reaction has dominated the advice given in the literature. However, in relation to the amount of admonition, the amount of objective information on the employment of diabetics is small. Brandaleone and Friedman (1953) found that of 63 firms in the United States who replied to a questionnaire, 43 employed diabetics but 33 of these restricted diabetics to occupations without hazards. The same authors analysed the records of more than 3,000 employees in a transport system in which were included 40 diabetics. They found that the accident and sickness absence rates of diabetics did not differ from those of other employees. A survey by the United States Department of Labor quoted by McKendry (1955) gave a similar finding, except that the sickness absence rate for diabetics was slightly elevated due to the prolonged absence of a few individuals. Beardwood (1950) quotes the experience of 18 years of 110 diabetics in a public utility company employing 7,000; the absenteeism of the diabetics was 33% below the average. Elstad (1946) gives the results of a follow-up of 154 men who were treated for diabetes in Norway between 1930 and 1939. Eighty-seven per cent of these required more than 20 units of insulin daily and half were classed as heavy workers. Eighty-seven per cent considered themselves completely fit for work and were continuing in their previous occupations, while 7·2% were partially fit, having been forced to change to a more suitable occupation.

The number of diabetics treated with insulin is probably higher among those of working age than among diabetics as a whole. Every diabetic on insulin is liable to have a hypoglycaemic reaction, irrespective of past experience, resulting from the introduction of new factors into his condition. The restrictions that should be placed upon a diabetic are of vital importance to the individual. Even as regards driving, there is no certainty of knowledge, for the *Lancet* (annotation, 1957) asks: " How dangerous is a diabetic in charge of a motor car?".

In this paper are reported the results of a survey designed to give an indication of the answers to these questions.

The Survey

During a period of four months, from August to November, 1957, patients attending the Diabetic Clinic

of the Dunedin Hospital were interviewed, and a form was completed by the interviewer. Of the 89 patients seen, one middle-aged woman declined the recording of the information given and has therefore been omitted from the survey. The age and sex composition of the survey group is shown in Table 1.

There is a preponderance of the older age groups, 61 patients being aged 46 years or more.

TABLE 1

AGE AND SEX OF SURVEY GROUP OF DIABETICS

Age	Male	Female	Total
Under 30	6	8	14
31 to 45	7	6	13
46 to 60	18	10	28
Over 60	17	16	33
Total	48	40	88

Results

Table 2 embodies the results obtained in the enquiries regarding occupation over the preceding five years. Occupations have been classified under five headings according to energy expenditure. Sedentary work is self-explanatory and includes clerical work and work done seated at machines. Ambulatory work involves

TABLE 2

OCCUPATIONAL STATUS, EMPLOYMENT HISTORY, AND RELATIONSHIP TO TREATMENT, HAZARDS, AND DISABILITIES

	Occupation (Present or Last Job)									
	Sedentary	Ambulatory	Light Manual	Medium Manual	Heavy Manual	Total Employed Group	Housewives	Retired	School Children	Total
Number of patients	21	15	7	9	2	54	21	12	1	88
Treatment										
On insulin :	13	12	5	4	2	36	11	8	1	56
No reactions	4	2	1	—	1	8	3	2	1	14
Mild reactions	6	9	2	2	1	20	5	5	—	30
Severe reactions	3	1	2	2	—	8	3	1	—	12
No insulin	8	3	2	5	—	18	10	4	—	32
Employment History in Past Five Years										
1. *No change:*										
Still in same job as before diagnosis	6	4	2	7	2	21				
Job begun since diagnosis	3	4	—	—	—	7				
Total no change	9	8	2	7	2	28				
2. *Permanently left Employment*										
Before diagnosis: Married						—				
Retired						3				
After diagnosis: Married						4				
Retired						3				
Total permanently left employment						10				
3. *Changed Job*‡										
Before diagnosis: Social reasons	1		←	1		2				
Ill-health		←		1	1*	2				
" Too hard "	←	1				1				
After diagnosis: Social reasons	2	1	→ 1							
	←			1		5				
Ill-health	2	1*								
		←		1		4				
"Too hard"		←		1		1				
"Too dangerous"	1			→		1				
Total changed job	6	3	1	6	—	16				
Liability to Hazards										
Machinery	3	1	3	2	1	10				
Heights	—	—	2	2	1	5				
Burns	—	—	1	—	—	1				
Total liable	3	1	6	4	2	16				
Lost Time—Industrial Conditions	—	—	1	—	1	2				
Other Illnesses and Disabilities										
Complications of diabetes:										
Disabling	2	3	1	3	—	9	5	5	—	19
Non-disabling	2	1	1	1	—	5	2	—	—	7
Complaints of tiredness	1	1	—	1	1	4	9	—	—	13
Unrelated conditions:										
Disabling	—	—	1	—	—	1	—	2	—	3
Non-disabling	3	1	—	—	1	5	4	3	—	12

*Unemployed at present time. †Driving has not been included.

‡Arrows show change of direction of type of occupation

continuous walking and standing without other significant expenditure of physical effort. Such workers as shop assistants, a police constable, a wool-classer, a charge attendant in a mental hospital, and a welfare officer are among those included in this category. The light manual workers include printers, painters, and bookbinders: medium manual work denotes such jobs as motor mechanic, builder, joiner, and labourer. The two heavy manual workers were employed as boilermaker and fireman. In allotting occupations to these categories, careful note was made of the actual nature of the job and its demands on the patient. This seemed to be more realistic than an arbitrary allocation of a particular job to a single category. An elderly woman living alone was classed as a housewife, but if she lived with relatives or in a home has been placed in the retired category.

Patients who left employment permanently during the five-year survey period are classified under the last occupations held. At the beginning of the survey period 54 patients (61·4%) were employed. In addition 21 (23·8%) were housewives, 12 (13·8%) had retired, and one was still at school. Ten of the employed group left their employment permanently during the survey period, four on marriage and six on retirement.

Thirty-six (66·6%) of the employed group were treated with insulin and 28 of these experienced reactions outside hospital. In eight cases, the reactions were severe, involving unconsciousness. In those not employed, 20 (60·0%) were on insulin and 14 of these had experienced reactions, four of them severely. Of those not on insulin, eight were under treatment by other medication at the time of interview, four of them in the employed group. These have not been considered separately from others not on insulin.

Over half the employed group were in the same occupation throughout the survey period, 21 in the same job that they had held before diagnosis and seven in jobs taken since diagnosis. Cases 1 and 2 are examples of those who remained in the same job.

Case 1.—J.A., a man, aged 47, a diabetic on insulin since the age of 32, has been a boilermaker for 30 years and works an average of 12 hours a week overtime. He experiences occasional mild reactions in the form of dizziness lasting a few minutes, for which he takes glucose. His recent absences from work have been due to a fractured toe and an operation (left mastectomy). He rides a bicycle and has never had an accident on it.

Case 2.—A.S., a man, aged 47, has taken insulin since the age of 33. For the last 11 years he has been a departmental manager in charge of 20 to 26 men. A sensation of tingling in the limbs presages occasional mild reactions. He drives a car at work and has had no accidents. He says that his only disadvantage is irregularity of meals while travelling. An early right cataract has been diagnosed this year.

Of the 16 who changed their jobs during the survey period, five did so before diagnosis, and 11 after the diagnosis of diabetes had been made. Social reasons accounted for two of the former and five of the latter changes.

At the time of interview, the following two patients were unemployed:

Case 3.—E.T., a man, aged 50, developed ulcers of the feet 16 months ago. Investigation revealed diabetes and he was treated with insulin. Before diagnosis he had been employed in the Public Service as a labourer for four years but has not worked since the ulcers developed. (Since these figures were abstracted, this man has returned to work.)

Case 4.—G.S., a man, aged 57, a diabetic on insulin since the age of 41, is subject to occasional mild reactions. He has been in receipt of social security benefit for two years on account of labyrinthine disturbances which caused him to leave his last occupation as shop assistant after one year. Before that he had been a driver but had to leave this work on account of angina following a coronary thrombosis in 1949. He was unemployed for a few months between these two jobs.

Of the remaining two changes made before diabetes was diagnosed, one was due to ill-health: the patient took a lighter job on the railway after a coronary thrombosis. In the second a policeman found a country job in sole charge too hard in view of the large garden for which he was responsible, and transferred to a sedentary job in the police force.

Apart from the patient still unemployed (Case 4), three others changed their occupation due to ill-health, after the diagnosis of diabetes was made, one on account of the onset of blindness which ended his clerical life: he is now employed on making cardboard boxes. Another changed to lighter work as a stores clerk after amputation of the right leg for gangrene. The third case is instructive:

Case 5.—S.M., a man, aged 46, was diagnosed and treated with insulin at the age of 40. At that time he was a building foreman but his employment on a variety of different tasks made him difficult to stabilize. Four years ago he became a building teacher and has had no reactions recently. He is still exposed to the hazards of machines and saws and drives a car without difficulty or accidents.

One man left his work because he considered it too hard:

Case 6.—J.C., a man, aged 48, a diabetic on insulin since the age of 29, was subject to occasional mild reactions in the early morning. Until 12 years ago he was a labourer in a butter factory. He found this too hard and spent the next 10 years on social security benefit. He was advised by his doctor to give this up and two years ago became a mess steward at which he has since been happily employed.

Another left his work because he considered it too dangerous:

Case 7.—R.B., a man, aged 23, on insulin since the age of 11, was subject to severe reactions, during which he is unconscious for a short time. These are preceded by a brief aura and have occurred four times in the last nine months. He was employed as a sedentary machinist but left nine months ago as he considered this work to be too dangerous although he had not had any accidents. He is now employed as a labourer. He rides a bicycle and has had no road accidents.

In the employed group of 54 patients, 10 are subject to hazards from machinery, five work at heights, and one is exposed to danger from burns. Two patients had lost

time in the last five years on account of industrial accidents: one was the boilermaker with a fractured toe (Case 1), a common accident in his trade, and the other was a painter who was blown off his ladder by the wind. There is therefore no evidence of an excess of industrial accidents among the diabetics included in this survey.

The final section of Table 2 shows the incidence of complications of diabetes and of unrelated conditions in the whole survey group. The complications of diabetes have been given a wide definition and the 19 disabling cases include five patients who share a common fundamental pathology of atheroma. Five cases have complications affecting the circulation in the legs and feet and three others have had insulin reactions of such severity as to require admission to hospital. Six patients have defects of vision, of whom three are blind. One of these has already been mentioned, and one is retired. The third case is described below:

Case 8.—D.B., a man, aged 30, on insulin since the age of 8, occasionally has mild reactions. He became blind (6/60 in both eyes) in 1950, before which he was employed as an accountant. This was followed by a period of unemployment and training at the Blind Institute. He has been usefully employed as a welfare officer for the blind for over five years.

A special note was made of complaints of tiredness where no other complication was found. No interrogation was made on this point and the complaints were all spontaneous. Four (7·4%) of the employed group and nine (36%) of the housewives volunteered this information.

Of the 25 housewives interviewed, four had married within the last five years. Among them they cared for 43 dependants (average 1·7 each) including five pre-school children. Three of the housewives were pregnant. The nine who complained of excessive tiredness cared for 22 dependants including four of the pre-school children, an average of 2·4 dependants each. None of the housewives employed help in the house, and tiredness may have been a complication of being a housewife with a family rather than a complication of diabetes.

In the retired group, which numbered 18 at the end of the enquiry, eight had retired before the diagnosis of diabetes was made, six on age, and two on account of ill-health. One patient retired on grounds of ill-health at the age of 69 after a series of operations including cholecystectomy and hemorrhaphy and the other at the age of 60 (four years before diagnosis) on account of unspecified ill-health after working long hours during the second war. One patient retired on age grounds in the year of diagnosis and nine have retired since the diagnosis of diabetes, four of them on grounds of age. Five retired on account of ill-health and in four of these diabetes or its complications was responsible. Details of these five cases are shown in Table 3.

Three of the eight patients who retired before the diagnosis of diabetes had been made were women; the five men in this group retired at an average age of 66 years. Of the nine patients who retired after diagnosis, two were women; the average age of the seven men on retirement was 65 years.

TABLE 3

RETIREMENT ON ACCOUNT OF ILL-HEALTH AFTER DIAGNOSIS OF DIABETES

Case No.	Age at Time of Enquiry (years)	Age at Diagnosis (years)	Age of Retirement (years)	Reason
9	72	66	66	Diabetes unspecified
10	78	55	72	Tuberculosis
11	70	58	59	Blindness
12	75	63	71	Age grounds but occasional severe reactions
13	60	55	57	Unspecified ill-health due to first war injuries

Apart from occupational details, questions were asked on three other points. The first two of these were suggested by the standards of employment of the American Diabetic Association and concerned the carriage of diabetic cards and the information given by the diabetic to his employer. At the Dunedin Clinic every patient on insulin is issued with a diabetic card. The answers given by patients on insulin to the question, "Do you carry your card?" are analysed in Table 4.

TABLE 4

CARRIAGE OF DIABETIC CARDS BY PATIENTS ON INSULIN

Card Carried		Always	Sometimes	Never
Total		24	8	24
Sex	Male	12	5	11
	Female	12	3	13
Age	Under 30	7	3	7
	31 to 45	5	2	8
	46 to 60	6	2	7
	Over 60	6	1	2
Reactions	None	6	1	2
	Mild	12	5	13
	Severe	6	2	4

Age, sex, and, surprisingly, liability to reactions appeared to have no relation to the carriage of a diabetic card by patients on insulin.

TABLE 5

KNOWLEDGE OF CONDITION BY EMPLOYER AND OTHER EMPLOYEES

Treatment Status	Condition					
	Known to Employer		Known to Employees			Not Applicable
	Yes	No	Yes	No	Not* Applicable	
On insulin	32	4	29	4	3	20
No insulin	31	2	13	4	1	14
Totals	63	6	42	8	4	34

* Works alone

Table 5 shows the answers obtained to questions on whether the diabetic state was known to the employer or fellow employees. Of the diabetics on insulin, four have kept their condition secret from both employer and fellow workers. All of these were subject to reactions, with a liability to unconsciousness in two cases.

continuous walking and standing without other significant expenditure of physical effort. Such workers as shop assistants, a police constable, a wool-classer, a charge attendant in a mental hospital, and a welfare officer are among those included in this category. The light manual workers include printers, painters, and bookbinders: medium manual work denotes such jobs as motor mechanic, builder, joiner, and labourer. The two heavy manual workers were employed as boilermaker and fireman. In allotting occupations to these categories, careful note was made of the actual nature of the job and its demands on the patient. This seemed to be more realistic than an arbitrary allocation of a particular job to a single category. An elderly woman living alone was classed as a housewife, but if she lived with relatives or in a home has been placed in the retired category.

Patients who left employment permanently during the five-year survey period are classified under the last occupations held. At the beginning of the survey period 54 patients (61·4%) were employed. In addition 21 (23·8%) were housewives, 12 (13·8%) had retired, and one was still at school. Ten of the employed group left their employment permanently during the survey period, four on marriage and six on retirement.

Thirty-six (66·6%) of the employed group were treated with insulin and 28 of these experienced reactions outside hospital. In eight cases, the reactions were severe, involving unconsciousness. In those not employed, 20 (60·0%) were on insulin and 14 of these had experienced reactions, four of them severely. Of those not on insulin, eight were under treatment by other medication at the time of interview, four of them in the employed group. These have not been considered separately from others not on insulin.

Over half the employed group were in the same occupation throughout the survey period, 21 in the same job that they had held before diagnosis and seven in jobs taken since diagnosis. Cases 1 and 2 are examples of those who remained in the same job.

Case 1.—J.A., a man, aged 47, a diabetic on insulin since the age of 32, has been a boilermaker for 30 years and works an average of 12 hours a week overtime. He experiences occasional mild reactions in the form of dizziness lasting a few minutes, for which he takes glucose. His recent absences from work have been due to a fractured toe and an operation (left mastectomy). He rides a bicycle and has never had an accident on it.

Case 2.—A.S., a man, aged 47, has taken insulin since the age of 33. For the last 11 years he has been a departmental manager in charge of 20 to 26 men. A sensation of tingling in the limbs presages occasional mild reactions. He drives a car at work and has had no accidents. He says that his only disadvantage is irregularity of meals while travelling. An early right cataract has been diagnosed this year.

Of the 16 who changed their jobs during the survey period, five did so before diagnosis, and 11 after the diagnosis of diabetes had been made. Social reasons accounted for two of the former and five of the latter changes.

At the time of interview, the following two patients were unemployed:

Case 3.—E.T., a man, aged 50, developed ulcers of the feet 16 months ago. Investigation revealed diabetes and he was treated with insulin. Before diagnosis he had been employed in the Public Service as a labourer for four years but has not worked since the ulcers developed. (Since these figures were abstracted, this man has returned to work.)

Case 4.—G.S., a man, aged 57, a diabetic on insulin since the age of 41, is subject to occasional mild reactions. He has been in receipt of social security benefit for two years on account of labyrinthine disturbances which caused him to leave his last occupation as shop assistant after one year. Before that he had been a driver but had to leave this work on account of angina following a coronary thrombosis in 1949. He was unemployed for a few months between these two jobs.

Of the remaining two changes made before diabetes was diagnosed, one was due to ill-health; the patient took a lighter job on the railway after a coronary thrombosis. In the second a policeman found a country job in sole charge too hard in view of the large garden for which he was responsible, and transferred to a sedentary job in the police force.

Apart from the patient still unemployed (Case 4), three others changed their occupation due to ill-health, after the diagnosis of diabetes was made, one on account of the onset of blindness which ended his clerical life: he is now employed on making cardboard boxes. Another changed to lighter work as a stores clerk after amputation of the right leg for gangrene. The third case is instructive:

Case 5.—S.M., a man, aged 46, was diagnosed and treated with insulin at the age of 40. At that time he was a building foreman but his employment on a variety of different tasks made him difficult to stabilize. Four years ago he became a building teacher and has had no reactions recently. He is still exposed to the hazards of machines and saws and drives a car without difficulty or accidents.

One man left his work because he considered it too hard:

Case 6.—J.C., a man, aged 48, a diabetic on insulin since the age of 29, was subject to occasional mild reactions in the early morning. Until 12 years ago he was a labourer in a butter factory. He found this too hard and spent the next 10 years on social security benefit. He was advised by his doctor to give this up and two years ago became a mess steward at which he has since been happily employed.

Another left his work because he considered it too dangerous:

Case 7.—R.B., a man, aged 23, on insulin since the age of 11, was subject to severe reactions, during which he is unconscious for a short time. These are preceded by a brief aura and have occurred four times in the last nine months. He was employed as a sedentary machinist but left nine months ago as he considered this work to be too dangerous although he had not had any accidents. He is now employed as a labourer. He rides a bicycle and has had no road accidents.

In the employed group of 54 patients, 10 are subject to hazards from machinery, five work at heights, and one is exposed to danger from burns. Two patients had lost

time in the last five years on account of industrial accidents: one was the boilermaker with a fractured toe (Case 1), a common accident in his trade, and the other was a painter who was blown off his ladder by the wind. There is therefore no evidence of an excess of industrial accidents among the diabetics included in this survey.

The final section of Table 2 shows the incidence of complications of diabetes and of unrelated conditions in the whole survey group. The complications of diabetes have been given a wide definition and the 19 disabling cases include five patients who share a common fundamental pathology of atheroma. Five cases have complications affecting the circulation in the legs and feet and three others have had insulin reactions of such severity as to require admission to hospital. Six patients have defects of vision, of whom three are blind. One of these has already been mentioned, and one is retired. The third case is described below:

Case 8.—D.B., a man, aged 30, on insulin since the age of 8, occasionally has mild reactions. He became blind (6/60 in both eyes) in 1950, before which he was employed as an accountant. This was followed by a period of unemployment and training at the Blind Institute. He has been usefully employed as a welfare officer for the blind for over five years.

A special note was made of complaints of tiredness where no other complication was found. No interrogation was made on this point and the complaints were all spontaneous. Four (7·4%) of the employed group and nine (36%) of the housewives volunteered this information.

Of the 25 housewives interviewed, four had married within the last five years. Among them they cared for 43 dependants (average 1·7 each) including five pre-school children. Three of the housewives were pregnant. The nine who complained of excessive tiredness cared for 22 dependants including four of the pre-school children, an average of 2·4 dependants each. None of the housewives employed help in the house, and tiredness may have been a complication of being a housewife with a family rather than a complication of diabetes.

In the retired group, which numbered 18 at the end of the enquiry, eight had retired before the diagnosis of diabetes was made, six on age, and two on account of ill-health. One patient retired on grounds of ill-health at the age of 69 after a series of operations including cholecystectomy and herniorrhaphy and the other at the age of 60 (four years before diagnosis) on account of unspecified ill-health after working long hours during the second war. One patient retired on age grounds in the year of diagnosis and nine have retired since the diagnosis of diabetes, four of them on grounds of age. Five retired on account of ill-health and in four of these diabetes or its complications was responsible. Details of these five cases are shown in Table 3.

Three of the eight patients who retired before the diagnosis of diabetes had been made were women; the five men in this group retired at an average age of 66 years. Of the nine patients who retired after diagnosis, two were women; the average age of the seven men on retirement was 65 years.

TABLE 3

RETIREMENT ON ACCOUNT OF ILL-HEALTH AFTER DIAGNOSIS OF DIABETES

Case No.	Age at Time of Enquiry (years)	Age at Diagnosis (years)	Age of Retirement (years)	Reason
9	72	60	63	Diabetes unspecified
10	78	55	73	Tuberculosis
11	70	58	59	Blindness
12	75	43	71	Age grounds but occasional severe reactions
13	60	55	57	Unspecified ill-health due to first war injuries

Apart from occupational details, questions were asked on three other points. The first two of these were suggested by the standards of employment of the American Diabetic Association and concerned the carriage of diabetic cards and the information given by the diabetic to his employer. At the Dunedin Clinic every patient on insulin is issued with a diabetic card. The answers given by patients on insulin to the question, " Do you carry your card? " are analysed in Table 4.

TABLE 4

CARRIAGE OF DIABETIC CARDS BY PATIENTS ON INSULIN

Card Carried		Always	Sometimes	Never
Total		24	8	24
Sex:	Males	12	5	11
	Females	12	3	13
Age:	Under 30	7	1	6
	31 to 45	3	3	4
	46 to 60	6	2	7
	Over 60	8	2	7
Reactions:	None	6	1	7
	Mild	12	5	13
	Severe	6	2	4

Age, sex, and, surprisingly, liability to reactions appeared to have no relation to the carriage of a diabetic card by patients on insulin.

TABLE 5

KNOWLEDGE OF CONDITION BY EMPLOYER AND OTHER EMPLOYEES

Treatment Status	Condition					Not Applicable
	Known to Employer		Known to Employees			
	Yes	No	Yes	No	Not* Applicable	
On insulin	32	4	29	4	3	20
No insulin	11	2	13	4	1	14
Totals	43	6	42	8	4	34

* Works alone.

Table 5 shows the answers obtained to questions on whether the diabetic state was known to the employer or fellow employees. Of the diabetics on insulin, four have kept their condition secret from both employer and fellow workers. All of these were subject to reactions, with a liability to unconsciousness in two cases.

Finally, the patients were asked whether or not they drove a motor vehicle or rode a bicycle and whether they had had any road accidents in the last five years. The answers are summarized in Table 6.

TABLE 6
DRIVING HABITS, INSULIN REACTIONS, AND ACCIDENTS IN LAST FIVE YEARS

	Insulin	No Insulin	Liability to Reactions of Patients on Insulin		
			Nil	Mild	Severe
Motor vehicles	18**	10**	4**	11	3
Bicycles	9	3	2	3	4
Pedestrians	29*	19	8*	16	5
Totals	56***	32**	14***	30	12

Total no. of accidents 5
No. of accidents to diabetics on insulin 3
*Accident on road (1 star = 1 accident).

Twenty-eight patients drove motor vehicles, two drove lorries, seven business cars, and the remainder private cars. Eighteen of the drivers took insulin and 14 of these were subject to reactions. Twelve, nine of them on insulin, rode bicycles. There were five accidents in the five-year survey period, three of them affecting insulin-treated diabetics. Two of these were drivers of business cars who drove a considerable mileage every year and one was a pedestrian who fell from a bus. The interesting point is that none of the patients involved in an accident was subject to insulin reactions.

Discussion

The main disadvantage of a survey of this type is the difficulty of assessing the reliability of the information provided. In each case the purpose of the survey was explained and it was emphasized that the name or address of the employer was not required. The attitude of the patients was such as to lead to no doubts of their veracity. Although the number of patients included is not large the age and sex representation is characteristic of diabetics as a whole.

No attempt has been made to estimate the insulin dosage of those so treated. Joslin, Root, White, and Marble (1952) have pointed out that the severity of an insulin reaction is by no means definitely commensurate with the extent of hypoglycaemia and it appears to be generally accepted that the dosage of insulin has no relationship to liability to reactions. Every diabetic on insulin may be considered to be liable to experience reactions. The facts elicited in this survey indicate that in nearly all cases occupation had not been materially affected even when insulin reactions occur. It is chiefly the complications of diabetes that have caused a change of occupation on medical grounds and generally this has been to lighter work, although not necessarily to work devoid of hazards, as indicated by Case 5. Case 6 shows that even cases which have been on social security benefit for several years can be satisfactorily settled in employment. There appears to be a tendency for diabetics to take sedentary work. Twenty-one of the 54 in the employed group were so employed, including six of the 21 who were still in the same job as before diagnosis. The national proportion employed in sedentary posts is unknown but the observation is interesting in view of the suggestion of Barach (1949) that " if a pair of identical twins, equally susceptible to diabetes, were so placed that one was to become a coal-miner and the other a clerk . . . , the one who earned his bread by the sweat of his brow would certainly not be the first to develop diabetes: better still he might not develop it at all ".

Although a number of the diabetics on insulin included in this survey were exposed to real hazards, the liability to insulin reactions did not appear to have affected the accident rate. None of the accidents reported appears to have had any relationship to an insulin reaction and it does not seem likely that this information was concealed when road accidents were readily reported. On the other hand the failure of four cases to reveal their condition to their employers may indicate a belief on their part that there is a prejudice against diabetics in industry.

Complaints of excessive tiredness were most evident among housewives. This might reflect the inability of the housewife to change her occupation if she feels her job is becoming too hard. No relationship was found between occupation as a causative factor and the incidence of other complications of diabetes. However, complications sometimes forced a change of employment, or incapacitated the patient in severe cases. This was especially true of eye and foot complications.

Many patients failed to carry diabetic cards, although this is a commonsense precaution. In the United States it has been recommended that the carriage of such cards by diabetics should be a prerequisite for employment. It would seem at least that more effort might be made by the medical profession to ensure that these cards are carried. An occasional re-issue of cards to all patients by the diabetic clinic would be one approach to this problem.

As far as the law is concerned, the diabetic driver has long been in a difficult position, and this has recently been made worse in the United Kingdom by a decision on appeal by the Divisional Court of the Queen's Bench Division (Armstrong v. Clark, 1957). The Lord Chief Justice stated that insulin was clearly a drug under the Road Traffic Act (1930), and continued by saying that if people were in a condition of health which either of itself rendered them liable to go into a coma or the remedies for which might send them into a coma, they must not drive because of the danger that would result to the rest of Her Majesty's subjects. No evidence of such danger was found in the present survey, which underlines the need for more objective data if diabetics are not to be unfairly penalized.

The public attitude to diabetics has been moulded by the medical profession, whose advice has been based on the assumption that patients should not be placed in a position in which they might injure themselves or others should an insulin reaction occur. While the evidence gathered in this survey is not conclusive because of the small number of cases involved, it suggests that many diabetics do place themselves in potentially dangerous positions; even if they had reactions, no harm appears to nave ensued to the patients surveyed. The assumption

made by the Lord Chief Justice and by many doctors that, where a person is liable to become unconscious, danger exists, is correct on strictly logical grounds. However, when all the characteristics of diabetes mellitus are considered, the position in respect of this disease is seen to be somewhat different.

The diabetic is not in the same category as many epileptics on whom complete unconsciousness is liable to descend with great suddenness. Most diabetics understand the mechanics of their condition fairly well: they know the time of day in which insulin reactions are liable to occur: they know how to treat reactions and usually carry sugar with them: and, most important of all, they usually have sufficient warning to take remedial measures before their consciousness becomes clouded. This applies even to many patients who have severe reactions. The patients who fail to wake in the morning are those in whom normal sleep has masked the premonitory signs and this has no influence on their employability, even if it may occasionally affect their punctuality.

Conclusion

It would appear, therefore, from this survey that many of the restrictions placed on diabetics are unnecessary: their potentiality for employment is limited solely by their stamina, by the presence of any organic complications of their disease, and by their own good sense. If these results are confirmed by other surveys, and the need for these is great, most diabetics should be freed from needless restrictions in the choice of their occupation.

I am indebted to Dr. J. A. Kilpatrick, physician of the Dunedin Hospital, for access to his patients and for his helpful advice and criticism in preparing this paper, and to Miss A. J. Smellie, public health nurse, for assistance in the collection of data, and to the Director-General of Health, New Zealand, for permission to publish.

References

American Diabetes Association (1952). Statement of the Committee on Employment. *Diabetes*, **1**, 336.
Annotation (1957). *Lancet*, **1**, 310.
Armstrong v. Clark (1957). " Medicine and the Law." *Ibid.*, **1**, 319.
Barach, J. H. (1949). *Diabetes and Its Treatment*, 1st. ed., p. 27. Oxford University Press, New York.
Beardwood, J. T. (1950). *Industr. Med. Surg.*, **19**, 271.
Brandaleone, H., and Friedman, G. J. (1953). *Diabetes*, **2**, 448.
Elstad, D. (1946). *Nord. Med.*, **31**, 1807.
Joslin, E. P., Root, H. F., White, P., and Marble A. (1952). *The Treatment of Diabetes Mellitus*, 9th ed., p. 309. Lea and Febiger, Philadelphia.
McKendry, J. B. R. (1955). *Occup. Hlth Rev.*, **6**, No. 2, p. 18.

Correction

In the article "Respiratory Function of Witwatersrand Goldminers: A Comparison between Radiologically Normal Miners and Control Non-mining Subjects" (Brit. J. industr. Med., **15**, 258) there is an error in Table 3 (p. 26), in the column "Fall in Compliance on Hyperventilation at f± 50/min.":—

51-60 years railway workers should be —0.019 not —0.083
S. D. should be 0.036 not 0.094

BOOK REVIEWS

A Short History of Public Health. By C. Fraser Brockington. (Pp. vii + 235. 15*s.*) London: J. & A. Churchill. 1956.

A reviewer is sometimes tempted to ask, Is this book really necessary ? The question is especially pertinent in this instance since, from Simon to Frazer, public health has been well served by its historians. A new version is, therefore, justified only if it offers a different approach or provides some new insights into the well-known narrative. Professor Fraser Brockington's latest book sets out to do this.

The book is divided into two parts; the first, which consists of a concise account of the history of public health in this country, provides the background for the second part, in which some of the major topics in this field are selected for fuller historical treatment and discussion.

On the whole the result is very satisfactory, although the book is not without its faults. The " short " history contained in Part I does not belie the title. The growth of public health during the past two centuries is covered in about 60 pages. This has involved a considerable degree of compression. In fact, compression has, at times, been carried too far and so given rise to such statements as that William Farr " observed the correlation between cholera and water supplies " (p. 25). A naïve student or a sophisticated statistician might gather from this that the incidence of cholera in an area is a function of the volume of water consumed or available. There are inaccuracies, too: the first medical officers of health in the Metropolitan districts were not "appointed on the instruction of the General Board of Health " (p. 24) but through the Metropolis Management Act of 1855; John Snow did not confront " the parish council " about the Broad Street pump (p. 25), it was the Board of Guardians. And, unfortunately, the hospital services today do not cost £300,000 (p. 60), but this may be a typographical error of which there are a number, especially in the index.

The second part, which occupies two-thirds of the book, is much better done, These eight chapters are devoted to the following subjects: the effects of economic and social changes on population, and the growth of community services for housing, maternal, and child health, neglected children, mental illness, tuberculosis, venereal disease, and the aged. In each case the historical account leads on to a discussion of current issues, which is both informative and thought-provoking.

Inevitably there are gaps. There is no mention of the school meals service and the free milk scheme in the chapter on the services for the child. This is perhaps to avoid duplicating the brief mention of these in Part I. Industrial health is not dealt with here, although the thread is woven into the general pattern of public health history in the first part.

The book is well written and is eminently readable. If the style is almost too colloquial at times, it sustains a lively interest throughout. Good use has been made of contemporary writings, and the quotations, of which there are a number, are particularly well chosen.

Despite its shortcomings, the book fully justifies itself. It provides a useful introductory text for the student and can be recommended for its lucid presentation of the historical setting of some of the principal public health problems of the present day.

S. P. W. CHAVE

Kwantitatieve benadering van het verzuim door Neurosen bij Nederlandse fabrieksarbeiders. By Meindert J. W. de Groot. (Pp.vii + 231; 12 figures.) Leiden: Nederlands Instituut voor Praeventieve Geneekunde. 1958.

This study of sickness absence attributable to neuroses is based mainly on data for three groups of workers, namely, (*a*) 57,000 employees of 31 industrial undertakings which submitted returns to the Netherlands Institute of Preventive Medicine (N.I.P.M.) for 1953; (*b*) 13,000 employees of Philips Works at Eindhoven for 1953; (*c*) 6,000 employees of the Royal Netherlands Iron and Steel Works for 1954.

Unfortunately different diagnostic groupings were applied to the data from each of these sources. The author has estimated the sickness absences in each group which would fall under the codes 310-318 of the International Statistical Classification, first from the distribution of the coding of the detailed diagnoses available with the N.I.P.M. data, and secondly from a study of the detailed case histories of samples of employees with neuroses from Philips and the Iron and Steel Works.

The N.I.P.M. data disclose an incidence of "definite neuroses" as defined in Russell Fraser's wartime study "The Incidence of Neurosis among Factory Workers", which is only about one sixth of Fraser's results for men and one quarter for women.

Within codes 310-318, the N.I.P.M. statistics show annual inception rates (spells) ranging from 8 to 12 per 1,000 men; the Philips data show rates of 8 per 1,000 men and 12 per 1,000 women. These results correspond closely with the experience of the London Transport Bus Overhaul Works, 1949-52, published in "Health in Industry" (1956). The iron and steel workers experienced a substantially higher rate of 45 per 1,000 men.

Examination of the samples of cases indicates that the above rates for Philips' employees may be underestimated and the rates for the iron and steel workers overestimated but that there is, nevertheless, a higher prevalence of serious neurotic disorders among the iron and steel workers.

The N.I.P.M. data falling in codes 310-318 show little variation of incidence with age, except that the rates are lower for the very youngest workers. The inception rates are higher for women than for men, especially at the younger ages. There is no evidence of seasonal variation.

One difficulty associated with this type of study is that it is of necessity related not to morbidity but to sickness absence, which is affected by the employee's criterion for stopping work, the medical standards of the employer, working conditions generally, and the financial consequences of sickness absence. Variations in these factors may give a false impression of changes in morbidity. The author compares the increase in absences attributable to non-functional disorders of the nervous system and sense organs, where the morbidity is unlikely to have altered substantially. He concludes that there is no evidence of an increased prevalence of neurosis.

Another difficulty lies in the lack of consistency of diagnosis. For a study of neuroses, particularly, the allocation of symptoms to a system of codes can be a major disturbing factor. The auther points out a number of serious defects in the International Statistical Classification in this respect. The impression given to the reader is that the problem is nearly insoluble, and this prompts the reflection that if separation of the symptoms does not in any event assist in a study of psychosomatic conditions, then in any broad grouping of diagnoses it would be better to relate symptoms to the associated physical diseases because this would undoubtedly aid the quantified analysis of the incidence of those diseases.

A third difficulty is the extension of the term "neurosis" to cover psychosociological troubles, not requiring treatment, among healthy people, the so-called "socioses". The author contends that these should be separated from morbid neurotic conditions but the reader may doubt whether this can in fact be done objectively.

This book is a valuable contribution to the literature, not only for the results achieved but as a study in methodology and an exposition of the philosophy underlying the analysis of sickness absence data.

C. J. CORNWALL

Practical Psychiatry for Industrial Physicians. By W. Donald Ross, M.D. (Pp. xx + 401. 57*s*. 6*d*.) Oxford: Blackwell Scientific Publications; Springfield (Illinois): Charles C. Thomas. 1956.

This is a much needed book, for although all physicians would be the better for some knowledge of psychiatry, the industrial physician needs it perhaps more than most. In spite of this, some mysterious occupational disease of those concerned with industrial medicine seems to cause them to be even more antagonistic to psychiatry than their colleagues in other branches of medicine. One could read through the books on occupational diseases, industrial hygiene, and the rest which have been published since the war without even suspecting that the worker possessed such a thing as a mind—except, of course, for the usual accounts of occupational cramps (do they still exist ?) and compensation neurosis.

Although the title of Professor Ross's book would seem to imply that he is solely concerned with the problem of mental disorders in industry, he in fact deals with a great deal more. He discusses absenteeism, accidents, fatigue, promotion, supervisors, trade unions, morale, the problems of new and old employees, of the woman worker, and—to delight the organically minded—neurological disabilities, head injuries, and industrial intoxications. The main emphasis, however, is on the everyday aspects of factory life, the everyday troubles of fairly ordinary people. He has written a useful com-

pendium of knowledge, not only of mental illness in industry, but of industrial psychology.

For the British reader the principal drawbacks of an otherwise excellent textbook are unavoidable owing to national differences: the problems of British trade unions, for example, are not those of American ones and alcoholism would hardly be considered a major problem amongst workers here as it appears to be in the United States. Addiction to neologisms is evident, such as " psychophysiologic " in place of " psychosomatic ".

One could wish, too, that Professor Ross, skilled as he is in the fields of psychiatry and psychology, might have recognized his limitations in the field of literature. Throughout his book are scattered quotations from the great—Plato, Shakespeare, Kipling, and Hippocrates, which, to say the least of it, are overworked. Presumably the point of introducing quotations is to produce a striking effect, but if they are such that even those with minimal knowledge can recognize them their point is wasted. One moves from " To be or not to be . . . ." to " Malt does more than Milton can to justify God's ways to man "; the whole gamut of the emotions (as Dorothy Parker once said) from A to B.

Professor Ross's book, so long as he keeps away from Eng. Lit., is a most valuable contribution to industrial medicine, and particularly so since on the whole it emphasizes the normal rather than the abnormal.

J. A. C. BROWN

Lavorazioni che espongono all'azione del Piombo-Tetraetile (n.19—Tabella delle Malattie Professionali). By G. Giuliano and M. Rafanelli. (Pp. 64; 11 figures.) Milan: Edizioni I.N.A.I.L. 1957.

This slim volume of 64 pages is the fifth of a series written under the general direction of a committee of chemists and published by the Italian National Institute for the Prevention of Industrial Accidents and Diseases. Works already published include (1) "Nitrous Fume"; (2) "Noise"; (3) "Carbon Disulphide"; (4) "Naphthalene and its Homologues", "Naphthols, Naphthylamines, and Halogenated, Sulphonated and Nitrated Derivatives of Naphthalene and its Homologues"; (5) "Tetraethyl Lead". The following are being prepared (6) "Phosgene"; (7) "Radiations"; (8) "Petrol and Petroleum Ether"; (9) "Glycol, Nitroglycerine, and their Derivatives".

The general physical and chemical properties, toxic action, and the maximum allowable concentration of lead tetraethyl are first described:

0·2 mg/m.³ produces evident symptoms in one hour.

0·1 mg/m.³ —0·14 mg/m.³ } is not tolerable for repeated exposures.

0·15 mg/m.³ is the American limit for an eight-hour working day but must not be regarded as more than the upper limit of toleration. In practice the atmospheric concentration should be well below this.

It is probably not generally known that lead tetraethyl was known over 100 years ago, its anti-knock properties being discovered only some 35 years ago. It is colourless, oily, strongly refractile, inflammable (yellow-orange flame with blue-green border), almost insoluble in water but easily soluble in fats, oils, and lipoid solvents. The lead in lead tetraethyl cannot be precipitated by alkalis but reacts with certain metallic and non-metallic chlorides and decomposes in the air and in sunlight.

The toxic effects depend upon the ready solubility of the compound in the lipoid of the central nervous system. The L.D. 50 for mice is about 3 p.p.m.; deaths occur between the 14th and 20th days of daily exposures to this concentration of 10 minutes.

Daily skin applications of 0·1 ml. to dogs lead to nervous symptoms and great depression on the 12th day and death on the 21st day.

Although the vapour pressure of tetraethyl lead is low, the important point for the toxicologist is that air saturated with it contains about 5 mg. lead per litre. Tetraethyl lead poisoning nowadays occurs among cleaners and repairers (skin absorption and inhalation) of storage tanks for leaded petrols. Symptoms include insomnia, anorexia, restlessness, asthenia, nausea, hallucinatory and exalted states. Signs include loss of weight, hypotension, vomiting, tremor, ataxia, psychomotor disturbances (for some recent cases see Walker and Boyd, 1952, *Lancet*, 1467). The hazards of manufacture and blending are apparent from the stages in the process, namely, preparation and reaction in an autoclave of ethyl chloride and a granulated Na-Pb alloy; transfer from autoclave to a still and steam distillation of tetraethyl lead; washing, mixing with a calculated amount of ethylene chloride or bromide and a dye; pumping of product to a decanting apparatus: filtration; automatic drumming in the open air.

From the nature of the reaction

$$4\ C_2H_5Cl + 4\ NaPb \rightarrow 4\ NaCl + Pb(C_2H_5)_4 + 3\ Pb$$

it is obvious that the lead remaining after distillation of the tetraethyl lead must be recovered from the sludges by removing the salt with water, fusing the lead, and casting it suitably for use in the preparation of fresh Na-Pb alloy. The authors, in an evaluation of the various hazards, give the general principles of safe working, illustrated by diagrams and photographs of process and plant, and give the M.A.C. for ethyl chloride as 1 p.p.m. which must be a mistake, but proper attention is drawn to the hazard of its escape carrying some tetraethyl with it from ducts, flanges, pumps, and storage vessels. In addition to the hazard of transfer of the alloy to the reactors, there is also the great hazard of temperature control in the latter. Safety pressure-valves, to obviate explosions, should discharge into stacks sufficiently wide and high to eliminate any possible danger to the plant and personnel.

The passage of the crude product from the horizontal reactor to the still below is, perhaps inevitably, attended by a certain very small diffusion of tetraethyl lead vapour into the atmosphere of the plant. Automatic control of temperature, pressure, and flow keeps the number of workers small but some operations must still be carried out by hand, *e.g.*, the emptying of the reactors, steam regulation and flow of cooling water, and above all, perhaps, the filling of drums. In an illustration of the latter operation a worker is shown, wearing long rubber gloves, top boots, overalls, and filter respirator. Automatic filling and weighing are followed by the delicate operation of emptying and detaching the filling pipe, the

whole operation being done either in the open air or in a strongly draughted chamber. The smallest splash of tetraethyl lead on a worker is immediately treated with petroleum and neutralized with $CaCl_2$.

Great stress is laid on the provision in the factory of a daily meal of about 1,700 calories; the rotation of workers so that intervals of 24 hours between exposure periods are assured; routine clinical and urinary examination; immediate treatment on the least sign of intoxication; provision of protective clothing and appliances, baths, showers; washing and sterilizing of working clothing; continuous chemical analysis of the atmosphere (the method is given for atmospheric samples, for biological liquids and for fuels).

With a discussion of the theory of anti-knock agents and of the hazards to be met with in places other than tetraethyl lead factories where leaded fuels are used, this monograph gives an indication of perhaps the most useful way in which the technology of hazardous industrial processes can be brought to practitioners of industrial medicine without over stress to the already busy mind.

M. W. GOLDBLATT

Industrial Toxicology, 2nd ed. By Lawrence T. Fairhall. (Pp. xii + 376. 80*s*.) London: Ballière, Tindall & Cox; Baltimore: The Williams & Wilkins Company. 1957.

The review of the first edition of this book (*Brit. J. industr. Med.*, 1950, **7**, 146) described it as an extremely valuable and well-documented summary of information on a great variety of compounds. The second edition has repaired some of the omissions to which attention was drawn in the above review.

While faults on matters of detail are easy to find in a book of this kind, the major criticism of this edition is that it is not up to date. Surprisingly perhaps, this applies especially to the sections on analytical methods, to which subject the author had made so many contributions. There is little reference to the literature after 1950. For example, there is no mention of modern and improved methods for estimating copper.

On the toxicological aspects, condensation is particularly difficult but on the whole an adequate picture is presented so that the reader gains the correct general impression of the potentialities of a particular compound. It is perhaps surprising to find that the author was still not convinced that beryllium itself is a toxic ion despite the wealth of experimental evidence to the contrary. His comparison between TEPP and parathion suggests that he was not fully conversant with the mode of action of these poisons. No reference is made to recent papers on nickel carbonyl or dimethylnitrosamine. It is difficult to see why a paper describing the ineffectiveness of BAL in treating experimental chloroform poisoning earned a niche. Clearly there is a place for a book of this kind and it is to be hoped that someone will take up the torch, for Dr. Fairhall's death was reported soon after this edition appeared.

J. M. BARNES

Particulate Clouds: Dusts, Smokes and Mists. Their Physics and Physical Chemistry and Industrial and Environmental Aspects. (Pp. xix+425; 8 plates and text figures. 70*s*.) London: E. & F. N. Spon. 1957.

A complete understanding of the behaviour of suspensions of fine droplets and particles in gases is a highly specialized study, demanding a wide knowledge of mathematical physics. The literature extends over a great many years and is widely scattered in journals and reports published in many parts of the world. Some of it is not readily accessible to the majority of workers, and the authors are to be congratulated in bringing together such a wealth of information in one book. They start by clarifying our ideas about the somewhat confusing terminology in this field, and make use of the term "particulate clouds" to describe "any type of suspension of particles in a gaseous medium regardless of the nature of the suspended material but excluding particles of such large size that they settle very rapidly." It is interesting to learn the original definition of the term aerosol, and to find a proper interpretation of the various uses of the word "smog".

Part I deals with the basic physics and physical chemistry of particulate clouds, covering their production, physical characteristics, optical properties, coagulation, deposition and filtration, sampling and estimation and diffusion into the atmosphere. It requires a fairly extensive knowledge of mathematics to follow through the theory presented in this section, but research workers and those engaged in the measurement of dust in industry will find within it a valuable exposition of the development of all types of sampling apparatus. The authors and their colleagues at Porton have in fact played a large part in this work, and whilst the research at this establishment was started primarily for defence purposes, this book illustrates how wide its applications have been.

Part II, which takes up approximately one-third of the text, illustrates the practical implications of Part I, and will be of more immediate interest to industrial workers. In Chapter 9 the principles of deposition and filtration dealt with earlier are applied to collecting plant such as cyclones, scrubbers, electrostatic precipitators, and ultrasonic agglomerators. The treatment is rather brief, but as in other chapters, many references are given. There is a useful table listing the filtering efficiencies of various types of dry fibrous filters. The chapter on health hazards occupies some 40 pages and deals chiefly with industrial dusts. The literature on inhalation and particle size is critically examined, and the need to consider the shape of particles as well as their size is mentioned. The individual protection of workers is considered in some detail, and the data given here on the performance of respirators is not easy to find elsewhere. Several pages are also devoted to the study of airborne infection. Chapter 11 summarizes observations which have been made on atmospheric pollution in Great Britain up to recent years and refers also to environmental studies carried out in America. The authors suggest that sulphuric acid mist should be considered as a potential toxic agent in smog. Chapter 12 deals with condensation nuclei and the drop size distribution in clouds and fog. The authors discuss experiments which have been carried out on the artificial nucleation of clouds, and consider methods of fog dissipation. They emphasize that although from a theoretical viewpoint fog dissipation by means of surface active agents may be

feasible, very little experimental evidence is available on which to judge whether such a technique would in fact be practicable.

Finally, there is a chapter on the practical uses of particulate clouds in industry and agriculture together with a brief reference to therapeutic uses. The preparation of screening and signal smokes in warfare is also dealt with. The reproduction in the eight plates is very good, although having them grouped together at the back of the book is a minor inconvenience.

R. E. WALLER

Traffic Accidents and Driver Characteristics: A Statistical and Psychological Study. By Sauli Häkkinen. (Pp. 198. $3.-.; 20*s*.) Helsinki: Institute of Technology.

This study, a thesis for the degree of Doctor of Technology, was carried out at the Institute of Occupational Health. Its main value lies in the full summary and review of the literature on this subject. The aim of the experimental study was "a general clarification of the characteristics requisite for a driver". The work is in two parts. The first is a statistical study of accident proneness in about 1,000 bus and tram drivers in Helsinki. It was found that such factors as age, driving experience, and duration of employment exerted a considerable influence upon accident rates. Correlations between the accidents in two consecutive years were in the order of 0·25 to 0·35 and between two consecutive four-year periods in the order of 0·6 to 0·7. The author concludes that a long period of observation, such as the eight years of the present study, is necessary for the consistency of accident rates to be sufficient for experimental use. This is a valuable warning to those whose periods of study of accident rates relate to only one or two years, or even less.

In the second part, 100 volunteer bus and tram drivers, in high and low accident groups, were subjected to a battery of intelligence, psychomotor personality, and mechanical aptitude tests. Although there was some variation between the test results, no single test appeared to be of practical value in differentiating between high and low accident groups. If multiple prediction by means of the five best test variables had been used for selection of drivers, the number of accidents would have been reduced by 34% if only 50% of the drivers had been accepted for employment. These valuable research studies should continue, but at present it is doubtful whether satisfactory practical tests of accident prediction are available for those who are engaged in driver selection.

L. G. NORMAN

Ergonomics. Human Factors in Work, Machine Control and Equipment Design, Vol. 1, No. 1, November, 1957. Edited by A. T. Welford. (Pp. 100; illustrated. 25*s*. per part, subscription £4 15*s*. 0*d*. per volume). London: Taylor and Francis, agents for Academic Press, New York.

Ergonomics, the title of this new quarterly journal, has been defined as the customs, habits, or laws of work. In the editorial article of this first number, it is pointed out that the problems of human work and of control operations which presented themselves in the last great war in relation to the equipment used in the fighting services are now known to have important implications for industry.

The first article in this number will be welcomed by many who drive cars and all who study road safety. Detailed examples are given of badly designed vehicles and it is urged that all possible faults in equipment and design as well as the capacities of the operator should be more fully studied before the vehicle takes the road.

In another paper a study is reported of the effects of noise on the behaviour of young naval ratings. In the conclusions reached it is suggested that because the effect of noise is often distracting rather than disabling, it may be more urgent to reduce irrelevant noise than that which is due to the work itself.

Elsewhere in this journal the traditional methods of training workpeople are contrasted with a new experimental method applied to those with the task of mending worsted cloth, an occupation which is rated in the Yorkshire wool textile industry as highly skilled. This new system of training is based on the theory that for the successful performance of a difficult task it is necessary to learn not only the correct method or motion pattern, but also to acquire the correct perception of the cues which make possible the desired motion pattern. This method has certain advantages over other better known training schemes and may be applicable in other industries.

Other papers contributed include studies of the causes of fatigue in drivers of high-speed diesel railway cars in the United States, of the changing physical demands made on German foundry workers, and of intermittent light stimulation and flicker sensation.

This journal, in which will be published papers relating to the human factors in work, machine control, and equipment design, has an editorial board representing several nations and is the official organ of the Ergonomics Research Society.

T. G. FAULKNER HUDSON

The Annals of Occupational Hygiene. (Pp. 133. £2 12*s*. 6*d*. per annum for private subscribers; £3 10*s*. per volume for libraries, industrial undertakings, and Government departments.) Published for the British Occupational Hygiene Society by the Pergamon Press, London. December, 1958.

The British Occupational Hygiene Society has initiated this new journal. Since its foundation a few years ago, brief reports of the Society's meetings have been welcomed for publication in the *British Journal of Industrial Medicine*, as have a number of the papers read at its meetings. The Society is now firmly established and naturally feels the need to have its own journal.

This first issue of the Annals is devoted to noise in industry. There are 11 authoritative papers, covering such aspects of the noise problem as the clinical and physiological effects of noise, noise measurement, noise suppression, the effects of noise on work, a study of occupational deafness, auditory damage after short exposure, and an account of the Scottish audiometer calibration service. A discussion is reported after several of the papers, though there is no mention of their having been read at a meeting. Busy readers may regret that only one paper is equipped with a summary.

The whole production is technically excellent. Wisely with a new journal, there is no commitment to publish a fixed number of issues annually.

Three main journals of occupational health are now published in Great Britain; perhaps one day both readers and editors might welcome amalgamation.

L. G. NORMAN

Books Received

(Review in a later issue is not precluded by notice here of books received.)

Report on the Health of the Royal Air Force and Women's Services of the Royal Air Force for the Year 1954 [A.P. 3319/54]. (92 roneod pp.; 10 charts, 26 tables.) London: Air Ministry. 1958.

Industrial Health Technology. By Bryan Harvey and Robert Murray. (Pp. xiii + 337; 78 figures. 45*s*.) London: Butterworth. 1958.

The Reliability of Statements About Smoking Habits [Tobacco Manufacturers' Standing Committee Research Papers No. 2]. By G. F. Todd and J. T. Laws. (50 foolscap pages.) London: Campbell-Johnson Ltd. 1958.

Diagnostic Performance Tests. By Boris Semeonoff and Eric Trist; Foreword by P. E. Vernon. (Pp. xv + 176; illustrated. 32*s*.) London: Tavistock Publications. 1958.

Rehabilitation of the Hand. By C. B. Wynn Parry. (Pp. vii + 272 + Index; 101 figures. 45*s*.) London: Butterworth. 1958.

The Preservation of Eyesight. By Sir Arthur Salusbury McNalty. (Pp. vii + 107; 9 figures. 12*s*. 6*d*.) Bristol: John Wright. 1958.

Occupational Allergy. Lectures held during a course on occupational allergy organized under the auspices of the European Academy of Allergy. (Pp. xvi + 329; illustrated. Florins 30.-.) Leiden: H. E. Stenfert Kroese N.V. 1958.

Digest of Statistics Analysing Certificates of Incapacity 1955/56. (Pp. 177, multigraphed double foolscap; 2 charts, 71 tables.) London: Ministry of Pensions and National Insurance. 1958.

Principles of Administration Applied to Nursing Service. By H. A. Goddard. (P. 106. 20*s*.) London: H. M. Stationery Office; Geneva; World Health Organization. 1958.

Recent Studies in Epidemiology. Edited by J. Pemberton and H. Willard. (Pp. xiii + 203; illustrated. 25*s*.) Oxford: Blackwell Scientific Publications. 1958.

Vore Almindelige Sygehuse og de Erhvervshaemmede (Need of Vocational Rehabilitation Among Patients Discharged from a Danish General Hospital). By K. H. Backer. (Pp. 306.) Copenhagen: Ejnar Munksgaard. 1958.

Expert Committee on Medical Rehabilitation: First Report [WHO Tech. Rep. Ser. No. 158]. (Pp. 52. 3*s*. 6*d*.) London: H.M. Stationery Office; Geneva: World Health Organization. 1958.

Air Pollution. Fifth Report of the Expert Committee on Environmental Sanitation [WHO Tech. Rep. Ser. No. 157]. (Pp. 26. 1*s*. 9*d*.) London: H.M. Stationery Office; Geneva: World Health Organization. 1958.

Health in Industry. By Donald Hunter. (Pp. 288; 18 plates. 4*s*.) Harmondsworth: Penguin Books. 1959.

Digest of Pneumoconiosis Statistics 1957. (20 multigraphed pages. 3*s*.) London: Ministry of Power. 1958.

Een onderzoek naar de asthmatische aard der Borstklachten van de Arbeiders in de Steenkolenmijnen (The Role of Asthmatic Predisposition in Coal Miners' Chest Complaints). By K. de Vries. (Pp. v + 124; 7 figures, 30 tables, 217 references.) Groningen: J. B. Wolters. 1958.

The National Corporation for the Care of Old People: Eleventh Annual Report for the Year ended 30th September, 1958. (Pp. 39.) London: Nuffield Foundation. 1959.

The Constituents of Tobacco Smoke: An Annotated Bibliography. Edited by H. R. Bentley and E. G. N. Berry [Tobacco Manufacturers' Standing Committee Research Papers No. 3]. (49 multigraphed foolscap pages.) London: Campbell-Johnson Ltd. 1959.

An Outline of Human Relationships. By Eustace Chesser. (Pp. 446. 25*s*.) London: Heinemann. 1959.

Films for Industry 1959-60. Catalogue prepared by Central Film Library. (Pp. 151; illustrated. 2*s*. 6*d*.) London: Central Office of Information. 1959.

The Pneumoconiosis Problem: With Emphasis on the Role of the Radiologist. By Eugene P. Pendergrass. (Pp. x + 146; 53 figures. 51*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1958.

Bulletin du Groupement d'Etude des Médecins du Travail des Ports [*Archives medico-chirurgicales de Normandie*, Numéro Special]. (Subscription for 10 numbers: Fr. fr. 500.-.) Strasbourg: Dr. A.-J. Chaumont. December, 1958.

The British Occupational Hygiene Society

An international symposium on inhaled particles and vapours, organized by the British Occupational Hygiene Society, will be held in Oxford in April, 1960, and will be concerned with the physical, chemical, and physiological factors governing the entry of harmful substances into the body via the respiratory system.

The subjects of the symposium will have a bearing on many hygiene problems including silicosis, asbestosis, and the other pneumoconioses, and on the damage to health produced by smog, tobacco smoke, radioactive gases and dusts, airborne bacteria, and toxic vapours.

Contributions will be welcomed from all countries. The main language will be English and it is intended to circulate the papers in advance in this language, but it is hoped to be able to provide interpretation for those contributions to the discussion which may be in French or German. Papers submitted will be subject to scrutiny by the Society's Honorary Editor, Dr. C. N. Davies, assisted by a panel of referees.

Those wishing to contribute are requested to notify the Chairman of the Organizing Committee, **Mr. W. H. Walton, Assistant Director, Mining Research Establishment, National Coal Board, Worton Hall, Worton Road, Isleworth, Middlesex,** as soon as possible, indicating the subject of their papers.

Whenever infection threatens–

'BRULIDINE'

trade mark *brand*

DIBROMOPROPAMIDINE ISETHIONATE CREAM

'Brulidine' contains dibromopropamidine the powerful antibacterial agent, which is active against common wound contaminants including the pyogenic cocci, *Bacterium coli*, *Pseudomonas pyocyanea*, and *Proteus vulgaris*. It is not an antibiotic, and shows little tendency to give rise to resistant pathogenic strains, whilst sensitization reactions are minimal.

'Brulidine' is equally indicated as a first aid dressing for minor burns, scalds and other injuries, and as a treatment for established surface infections due to susceptible organisms.

PRESENTATIONS: 0·15% cream in a water miscible base in tubes of 1 oz. and containers of 1 lb.

Detailed information is available on request.

MANUFACTURED BY MAY & BAKER LTD

MA5923.100

An **M&B** *brand Medical Product*

DISTRIBUTORS: PHARMACEUTICAL SPECIALITIES (MAY & BAKER) LTD · DAGENHAM

FOR

SUB-ACUTE and Chronic dermatoses

TAR + HYDROCORTISONE

combined in

TARCORTIN

CREAM

have pronounced advantages over either medicament alone

The established germicidal, stimulating and anti-pruritic properties of tar, in the treatment of sub-acute and refractory skin affections, can now be considerably enhanced by its incorporation with hydrocortisone. *Clinical trials have shown that the two medicaments together exert a powerful synergistic action that is far more rapid, more pronounced and complete than the action of either alone. These two valuable therapeutic agents are presented in a non-greasy, stainless, hydrophilic cream, known as TARCORTIN.

TARCORTIN CREAM

is supplied in 7 grm. and 15 grm. tubes, containing 0.5% Hydrocortisone in a special coal-tar extract.

***Literature available on request.**

STAFFORD-MILLER LIMITED · HATFIELD · HERTS

Manufacturing Chemists

By arrangement with Reed & Carnrick, Jersey City, U.S.A. (Est. 1860)

An Invaluable X-Ray Service

to Industrial Medical Officers throughout the Country

Please write stating your requirements for quotation or ask our representative to call

Above is an illustration of our new Mobile X-Ray Unit. The X-Ray apparatus is equipped with the latest 400 m.a. rotating anode tube, thereby ensuring full-size chest films of the highest quality.

The Service includes:

Chest examinations of workers on site.

Periodical visits at monthly or other intervals.

New entrants examined at frequent periods.

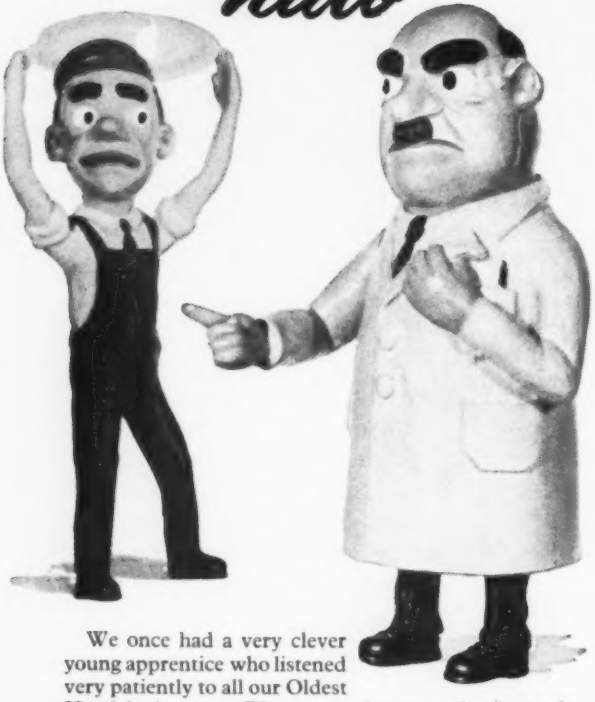
Nightshift workers X-rayed during working hours.

Annual survey of entire staff.

PORTABLE X-RAYS LIMITED

Power Road, Chiswick, London, W.4. Tel.: CHIswick 7836/7

Hexachlorophene halo



We once had a very clever young apprentice who listened very patiently to all our Oldest Hand had to say. Then, out of pure enthusiasm, the lad went to the lab, verified the formula for our barrier cream, and finally announced.

"What you tell me about Hexachlorophene is absolutely right. It really is such a fine protection against bacteria. I shall use nothing else but Sternocleanse from now on to guard against dermatitis."

Speechless, our O.H. patted the lad's head. Then he tottered away, muttering.

"I wash my 'ands of 'im, I really do . . ."

Sternol

Sternocleanse barrier cream

STERNOL LIMITED
ROYAL LONDON HOUSE, FINSBURY SQUARE, LONDON E.C.2
Tel.: MONarch 3871-5

INDUSTRIAL CLEANLINESS

SAROUL gives 24 hour protection to hands & skin

Adequate protection is ensured by using Saroul after work—it is scientifically compounded to remove grime and dirt quickly and completely. It is not a harsh antiseptic but a cleansing agent which assists the natural healing processes and extends its protective effect for many hours. Saroul is a positive safeguard against industrial dermatitis.

Testing samples and literature Free on request to Dept. BS.

SAROUL Antiseptic Hand Cleanser is made by

Sandeman Brothers Ltd.
BILSLAND DRIVE · MARYHILL · GLASGOW

DIPLOMA IN INDUSTRIAL HEALTH *of the* SOCIETY OF APOTHECARIES OF LONDON

The Society of Apothecaries of London, conscious of the paramount importance of an efficient health service in Industry, has instituted this Diploma in Industrial Health, which is of a very high standard and is open to registered medical practitioners, members of H.M. Services, and others, such as Examining Surgeons, etc.

The Examination—which consists of three Papers, Oral and Clinical — is held in July and December.

The next Examination begins on July 13th, 1959.

Regulations and Forms of Application for Admission to the Examinations may be obtained from

The Registrar,
SOCIETY OF APOTHECARIES OF LONDON
BLACK FRIARS LANE, E.C.4

EMERGENCIES IN GENERAL PRACTICE

This book comprises 57 specially commissioned articles on medical emergencies which appeared originally in the *British Medical Journal*.

Contents include haemorrhage and thrombosis, cardio-respiratory crises, anaesthesia and hazards of therapy, acute abdominal cases, obstetrics, fits and coma, electrocution, burns and gassing, poisoning, acute psychiatric states, and special and minor surgery.

Invaluable to all doctors everywhere.

470 *pages, cloth bound with full index.* 25*s. net* (*by post—inland and overseas* 26*s.* 9*d.*).

CLINICAL PATHOLOGY IN GENERAL PRACTICE

This handbook on clinical pathology meets the needs of the general practitioner, the houseman, and the senior student. It contains thirty-nine articles comprising a series specially written for the *British Medical Journal*. Each article has been revised and brought up-to-date by its author. The book gives authoritative information on available laboratory facilities; reliable tests and which to use; techniques for collecting and preserving specimens; interpretation of results and significance of abnormal findings.

321 *pages. Price* 21*s.* (*by post—inland and overseas* 22*s.* 3*d.*).

REFRESHER COURSE FOR GENERAL PRACTITIONERS

Second Collection

Third Collection—with Classified Contents List to volumes 1, 2 and 3

Each book contains a collection of sixty Refresher Course articles from the *British Medical Journal*. Each article, written by an acknowledged expert, has been revised by its author. The articles cover a wide range. Their object is to refresh the reader's memory of what is old and well-established and to tell him about new developments.

They are invaluable to general practitioners and residents as practical reference books, to specialists as a means of keeping in touch with developments outside their own field, and to final-year students as up-to-date and reliable textbooks.

25*s. each* (*by post—inland and overseas* 26*s.* 9*d.*).

"ANY QUESTIONS?"

Second Series

Third Series—with Cumulative Index

These pocket-size volumes each contain some 200 questions and expert answers from the "Any Questions?" pages of the *British Medical Journal*. Each answer has been chosen for its practical value to doctors in their day-to-day work. Many deal with subjects not covered in the standard textbooks.

The Third volume has a cumulative index to all the answers appearing in the three books in the series.

7*s.* 6*d. each* (*by post* 8*s.* 3*d.*).

Obtainable from booksellers or by post from

BRITISH MEDICAL ASSOCIATION

B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1

Hexachlorophene halo

We once had a very clever young apprentice who listened very patiently to all our Oldest Hand had to say. Then, out of pure enthusiasm, the lad went to the lab, verified the formula for our barrier cream and finally announced:

"What you tell me about Hexachlorophene is absolutely right. It really is such a fine protection against bacteria I shall use nothing else but Sternocleanse from now on to guard against dermatitis."

Speechless, our O.H. patted the lad's head. Then he tottered away, muttering,

"I wash my 'ands of 'im. I really do . . ."

Sternol *Sternocleanse barrier cream*

STERNOL LIMITED
ROYAL LONDON HOUSE, FINSBURY SQUARE, LONDON E.C.2
Tel: MONarch 3871-5

INDUSTRIAL CLEANLINESS

SAROUL gives 24 hour protection to hands & skin

Adequate protection is ensured by using Saroul after work—it is scientifically compounded to remove grime and dirt quickly and completely. It is not a harsh antiseptic but a cleansing agent which assists the natural healing processes and extends its protective effect for many hours. Saroul is a positive safeguard against industrial dermatitis.

Testing samples and literature Free on request to Dept. BS

SAROUL Antiseptic Hand Cleanser is made by

Sandeman Brothers Ltd.
BILSLAND DRIVE MARYHILL GLASGOW

DIPLOMA IN INDUSTRIAL HEALTH *of the* SOCIETY OF APOTHECARIES OF LONDON

The Society of Apothecaries of London, conscious of the paramount importance of an efficient health service in Industry, has instituted this Diploma in Industrial Health, which is of a very high standard and is open to registered medical practitioners, members of H.M. Services, and others, such as Examining Surgeons, etc.

The Examination—which consists of three Papers, Oral and Clinical — is held in July and December.

The next Examination begins on July 13th, 1959.

Regulations and Forms of Application for Admission to the Examinations may be obtained from

The Registrar,
SOCIETY OF APOTHECARIES OF LONDON
BLACK FRIARS LANE, E.C.4

EMERGENCIES IN GENERAL PRACTICE

This book comprises 57 specially commissioned articles on medical emergencies which appeared originally in the *British Medical Journal*.

Contents include haemorrhage and thrombosis, cardio-respiratory crises, anaesthesia and hazards of therapy, acute abdominal cases, obstetrics, fits and coma, electrocution, burns and gassing, poisoning, acute psychiatric states, and special and minor surgery.

Invaluable to all doctors everywhere.

470 *pages, cloth bound with full index.* 25*s. net* (*by post—inland and overseas* 26*s.* 9*d.*).

CLINICAL PATHOLOGY IN GENERAL PRACTICE

This handbook on clinical pathology meets the needs of the general practitioner, the houseman, and the senior student. It contains thirty-nine articles comprising a series specially written for the *British Medical Journal*. Each article has been revised and brought up-to-date by its author. The book gives authoritative information on available laboratory facilities; reliable tests and which to use; techniques for collecting and preserving specimens; interpretation of results and significance of abnormal findings.

321 *pages. Price* 21*s.* (*by post—inland and overseas* 22*s.* 3*d.*).

REFRESHER COURSE FOR GENERAL PRACTITIONERS

Second Collection

Third Collection—with Classified Contents List to volumes 1, 2 and 3

Each book contains a collection of sixty Refresher Course articles from the *British Medical Journal*. Each article, written by an acknowledged expert, has been revised by its author. The articles cover a wide range. Their object is to refresh the reader's memory of what is old and well-established and to tell him about new developments.

They are invaluable to general practitioners and residents as practical reference books, to specialists as a means of keeping in touch with developments outside their own field, and to final-year students as up-to-date and reliable textbooks.

25*s. each* (*by post—inland and overseas* 26*s.* 9*d.*).

"ANY QUESTIONS?"

Second Series

Third Series—with Cumulative Index

These pocket-size volumes each contain some 200 questions and expert answers from the "Any Questions?" pages of the *British Medical Journal*. Each answer has been chosen for its practical value to doctors in their day-to-day work. Many deal with subjects not covered in the standard textbooks.

The Third volume has a cumulative index to all the answers appearing in the three books in the series.

7*s.* 6*d. each* (*by post* 8*s.* 3*d.*).

Obtainable from booksellers or by post from

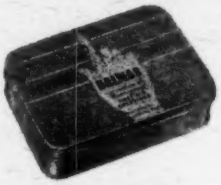
BRITISH MEDICAL ASSOCIATION

B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1

3 DALMAS ESSENTIALS for Industrial Welfare

DALMAS WATERPROOF DRESSINGS . . .

repel water, oil, acid, keep the wound *safe* under dirty conditions. In the Doctor's Cabinet—180 in seven sizes and shapes, with 1 yd. Dalmas Strapping.



SEAL-WRAPPED DRESSINGS . . .

Waterproof or elastic. Individually hygienically wrapped. In various sizes in handy packs. Indispensable in the first-aid room. Easily carried to site of work and ideal to take home for the week-end.

DUMB-BELL SUTURES . . .

used instead of stitching in minor surgery. Easily applied, instantly adhesive, extremely effective in keeping the wound closed. Packets of 6 dozen Sutures.

Samples and literature gladly supplied on request

DALMAS LTD., LEICESTER

DALMAS PROTECTION PREVENTS INFECTION!!

SPECIALIST JOURNALS

ANNALS OF THE RHEUMATIC DISEASES
Quarterly. Annual Subscription, £3.

ARCHIVES OF DISEASE IN CHILDHOOD
Bi-monthly. Annual Subscription, £4 4s.

BRITISH HEART JOURNAL
Quarterly. Annual Subscription, £3.

BRITISH JOURNAL OF INDUSTRIAL MEDICINE
Quarterly. Annual Subscription, £3.

BRITISH JOURNAL OF PHARMACOLOGY AND CHEMOTHERAPY
Quarterly. Annual Subscription, £4 4s.

BRITISH JOURNAL OF PREVENTIVE AND SOCIAL MEDICINE
Quarterly. Annual Subscription, £3.

BRITISH JOURNAL OF VENEREAL DISEASES
Quarterly. Annual Subscription, £3.

JOURNAL OF CLINICAL PATHOLOGY
Bi-monthly. Annual Subscription, £4 4s.

JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
Quarterly. Annual Subscription, £3.

MEDICAL AND BIOLOGICAL ILLUSTRATION
Quarterly. Annual Subscription, £3.

THORAX
Quarterly. Annual Subscription, £3.

BRITISH JOURNAL OF OPHTHALMOLOGY
Monthly. Annual Subscription, £6.

OPHTHALMIC LITERATURE
Six issues and index yearly. Annual Subscription £4 4s.
Combined subscription with British Journal of Ophthalmology, £9.

BRITISH MEDICAL ASSOCIATION
B.M.A. House, Tavistock Square, London, W.C.1

Dermatitis accounts for over 50% of lost 'man hours'

The Annual Report of the Chief Inspector of Factories shows that dermatitis accounts for more than half the time lost because of occupational disease by those in insurable employment. Yet dermatitis can be controlled by using the appropriate Rozalex Barrier Cream for the work involved. These barrier creams have been accepted as the standard preparations for over 25 years by those concerned with occupational health. The severity of the skin risk varies with the trade, but in all occupations there is a need for protection and cleanliness. Full technical resources are available on request to Rozalex Ltd., 10 Norfolk Street, Manchester 2.

Protect hands with

ROZALEX BARRIER CREAMS

R112 B

PRINTED IN ENGLAND BY THE THANET PRESS, MARGATE